(54) Title: INHIBITORS OF PRENYL–PROTEIN TRANSFERASE

(57) Abstract

The present invention comprises piperazine–containing compounds which inhibit prenyl–protein transferases, including farnesyl–protein transferase and geranylgeranyl–protein transferase type I. Such therapeutic compounds are useful in the treatment of cancer.

TITLE OF THE INVENTION
INHIBITORS OF PRENYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

5   The present invention relates to certain compounds that are useful for the inhibition of prenyl-protein transferases and the treatment of cancer. In particular, the invention relates to prenyl-protein transferase inhibitors which are efficacious in vivo as inhibitors of geranylgeranyl-protein transferase type I

10   (GGTase-I) and that inhibit the cellular processing of both the H-Ras protein and the K4B-Ras protein.

          Prenylation of proteins by prenyl-protein transferases represents a class of post-translational modification (Glomset, J. A., Gelb, M. H., and Farnsworth, C. C. (1990). Trends Biochem. Sci.

15   15, 139-142; Maltese, W. A. (1990). FASEB J. 4, 3319-3328). This modification typically is required for the membrane localization and function of these proteins. Prenylated proteins share characteristic C-terminal sequences including CAAX (C, Cys; A, an aliphatic amino acid; X, another amino acid), XXCC, or XCXC.

20   Three post-translational processing steps have been described for proteins having a C-terminal CAAX sequence: addition of either a 15 carbon (farnesyl) or 20 carbon (geranylgeranyl) isoprenoid to the Cys residue, proteolytic cleavage of the last 3 amino acids, and methylation of the new C-terminal carboxylate (Cox, A. D. and

25   Der, C. J. (1992a). Critical Rev. Oncogenesis 3:365-400; Newman, C. M. H. and Magee, A. I. (1993). Biochim. Biophys. Acta 1155:79-96). Some proteins may also have a fourth modification: palmitoylation of one or two Cys residues N-terminal to the farnesylated Cys. While some mammalian cell proteins

30   terminating in XCXC are carboxymethylated, it is not clear whether carboxy methylation follows prenylation of proteins terminating with a XXCC motif (Clarke, S. (1992). Annu. Rev. Biochem. 61, 355-386). For all of the prenylated proteins, addition of the isoprenoid is the first step and is required for the

subsequent steps (Cox, A. D. and Der, C. J. (1992a). Critical Rev. Oncogenesis 3:365-400; Cox, A. D. and Der, C. J. (1992b) Current Opinion Cell Biol. 4:1008-1016).

5   Three enzymes have been described that catalyze protein prenylation: farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). These enzymes are found in both yeast and mammalian cells (Clarke, 1992; Schafer, W. R. and Rine, J. (1992)

10   Annu. Rev. Genet. 30:209-237). Each of these enzymes selectively uses farnesyl diphosphate or geranyl-geranyl diphosphate as the isoprenoid donor and selectively recognizes the protein substrate. FPTase farnesylates CaaX-containing proteins that end with Ser, Met, Cys, Gln or Ala. For FPTase, CaaX tetrapeptides comprise

15   the minimum region required for interaction of the protein substrate with the enzyme. The enzymological characterization of these three enzymes has demonstrated that it is possible to selectively inhibit one with little inhibitory effect on the others (Moores, S. L., Schaber, M. D., Mosser, S. D., Rands, E., O'Hara, M.

20   B., Garsky, V. M., Marshall, M. S., Pompliano, D. L., and Gibbs, J. B., J. Biol. Chem., 266:17438 (1991), U.S. Pat. No. 5,470,832).

The prenylation reactions have been shown genetically to be essential for the function of a variety of proteins (Clarke, 1992; Cox and Der, 1992a; Gibbs, J. B. (1991). Cell 65: 1-4;

25   Newman and Magee, 1993; Schafer and Rine, 1992). This requirement often is demonstrated by mutating the CaaX Cys acceptors so that the proteins can no longer be prenylated. The resulting proteins are devoid of their central biological activity. These studies provide a genetic "proof of principle" indicating

30   that inhibitors of prenylation can alter the physiological responses regulated by prenylated proteins.

The Ras protein is part of a signaling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical

studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation, Ras is induced to exchange GDP for GTP and undergoes a conformational change.

5   The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, Ann. Rev. Biochem. 62:851-891 (1993)). Activation of Ras leads to activation of

10   multiple intracellular signal transduction pathways, including the MAP Kinase pathway and the Rho/Rac pathway (Joneson et al., Science 271:810-812).

Mutated ras genes are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma,

15   and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

The Ras protein is one of several proteins that are known to undergo post-translational modification. Farnesyl-

20   protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss et al., Cell, 62:81-88 (1990); Schaber et al., J. Biol. Chem., 265:14701-14704 (1990); Schafer et al., Science, 249:1133-1139 (1990); Manne et al., Proc. Natl. Acad. Sci USA, 87:7541-7545

25   (1990)).

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of

30   Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa[1]-Aaa[2]-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen et al., Nature 310:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-

protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C_{15} or C_{20} isoprenoid, respectively. (S. Clarke., Ann. Rev. Biochem. 61:355-386 (1992); W.R. Schafer and J. Rine, Ann. Rev.

5   Genetics 30:209-237 (1992)). Direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

Other farnesylated proteins include the Ras-related

10   GTP-binding proteins such as RhoB, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., J. Biol. Chem. 269, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of

15   unknown structure and function in addition to those listed above.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first class includes analogs of farnesyl diphosphate (FPP), while the second is related to protein substrates (e.g., Ras) for the enzyme. The

20   peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber et al., ibid; Reiss et. al., ibid; Reiss et al., PNAS, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as

25   alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl et al., Science, 260:1934-1937 (1993); Graham, et al., J. Med. Chem., 37, 725 (1994)).

Mammalian cells express four types of Ras proteins

30   (H-, N-, K4A-, and K4B-Ras) among which K4B-Ras is the most frequently mutated form of Ras in human cancers. The genes that encode these proteins are abbreviated H-ras, N-ras , K4A-ras and K4B-ras respectively. H-ras is an abbreviation for Harvey-ras. K4A-ras and K4B-ras are abbreviations for the Kirsten splice

variants of ras that contain the 4A and 4B exons, respectively.
Inhibition of farnesyl-protein transferase has been shown to block
the growth of H-ras-transformed cells in soft agar and to modify
other aspects of their transformed phenotype. It has also been

5   demonstrated that certain inhibitors of farnesyl-protein
transferase selectively block the processing of the H-Ras
oncoprotein intracellularly (N.E. Kohl et al., Science, 260:1934-
1937 (1993) and G.L. James et al., Science, 260:1937-1942 (1993).
Recently, it has been shown that an inhibitor of farnesyl-protein

10   transferase blocks the growth of H-ras-dependent tumors in nude
mice (N.E. Kohl et al., Proc. Natl. Acad. Sci U.S.A., 91:9141-9145
(1994) and induces regression of mammary and salivary
carcinomas in H-ras transgenic mice (N.E. Kohl et al., Nature
Medicine, 1:792-797 (1995).

15   Indirect inhibition of farnesyl-protein transferase in
vivo has been demonstrated with lovastatin (Merck & Co.,
Rahway, NJ) and compactin (Hancock et al., ibid; Casey et al.,
ibid; Schafer et al., Science 245:379 (1989)). These drugs inhibit
HMG-CoA reductase, the rate limiting enzyme for the production

20   of polyisoprenoids including farnesyl pyrophosphate. Inhibition
of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA
reductase blocks Ras membrane localization in cultured cells.

               It has been disclosed that the lysine-rich region and
terminal CVIM sequence of the C-terminus of K-RasB confer

25   resistance to inhibition of the cellular processing of that protein
by certain selective FPTase inhibitors. James, et al., J. Biol.
Chem. 270, 6221 (1995) Those FPTase inhibitors were effective in
inhibiting the processing of H-Ras proteins. James et al.
suggested that prenylation of the K4B-Ras protein by GGTase-I

30   contributed to the resistance to the selective FPTase inhibitors.

               Selective inhibitors of GGTase-I have been previously
disclosed (see for example U.S. Pat. No. 5,470,832, issued
November 28, 1995). Other compounds have been described as
selective inhibitors of GGTase-I (see for example PCT Publication

No. WO 96/21456). Combinations of a selective inhibitor of FPTase
and a selective inhibitor of GGTase-I have been disclosed as
useful in the treatment of cancer (PCT Publication No. WO
97/34664).

5   Several groups of scientists have recently disclosed
compounds that are non-selective FPTase/GGTase-I inhibitors.
(Nagasu et al. Cancer Research, 55:5310-5314 (1995); PCT
application WO 95/25086).

         It is the object of the instant invention to provide a
10 prenyl-protein transferase inhibitor which is efficacious in vivo
as an inhibitor of geranylgeranyl-protein transferase type I
(GGTase-I), also known as CAAX GGTase.

         It is also the object of the present invention to provide
a compound which inhibits the cellular processing of both the H-
15 Ras protein and the K4B-Ras protein.

         It is also the object of the present invention to provide
a compound which is efficacious in vivo as an inhibitor of the
growth of cancer cells characterized by a mutated K4B-Ras
protein.

20   A composition which comprises such an inhibitor
compound is used in the present invention to treat cancer.

SUMMARY OF THE INVENTION

         The present invention comprises piperazine-
25 containing compounds which inhibit prenyl-protein transferases.
Further contained in this invention are chemotherapeutic
compositions containing these prenyl transferase inhibitors and
methods for their production.

30   The compounds of this invention are illustrated by the
formula A:

$$V - A^1(CR^{1a}_2)_nA^2(CR^{1a}_2)_n - \left(\overset{(R^9)_q}{\underset{}{W}}\right)_t -(CR^{1b}_2)_p-\overset{R^2}{\underset{R^3\,R^4}{\overset{|}{N}}}\overset{G}{\underset{(\,)_s}{\overset{\|}{C}}}N-A^3(CR^{1c}_2)_vA^4Z$$

with $(R^8)_r$ attached above V.

A
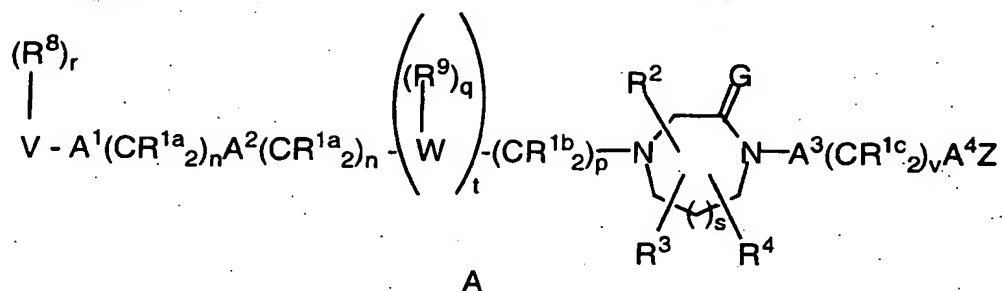
DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the
inhibition of prenyl-protein transferases and the prenylation of
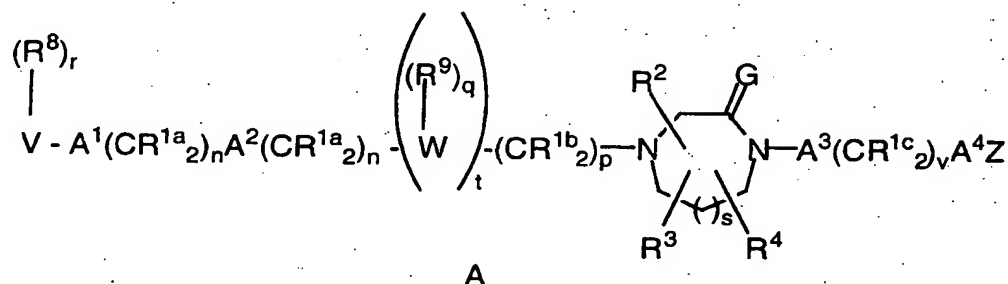the oncogene protein Ras. In a first embodiment of this
invention, the inhibitors of prenyl-protein transferases are
illustrated by the formula A:

$$V - A^1(CR^{1a}_2)_nA^2(CR^{1a}_2)_n - \left(\overset{(R^9)_q}{\underset{}{W}}\right)_t -(CR^{1b}_2)_p-\overset{R^2}{\underset{R^3\,R^4}{\overset{|}{N}}}\overset{G}{\underset{(\,)_s}{\overset{\|}{C}}}N-A^3(CR^{1c}_2)_vA^4Z$$

with $(R^8)_r$ attached above V.

A

wherein:

R^{1a} and R^{1b} are independently selected from:
- a)   hydrogen,
- b)   aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl,
  C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-,
  $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, NO$_2$, $R^{10}C(O)$-,
  N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
- c)   unsubstituted or substituted C_1-C_6 alkyl wherein the
  substitutent on the substituted C_1-C_6 alkyl is selected

from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{1c} is independently selected from:
   a)   hydrogen,
   b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,
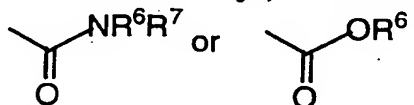   c)   unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$ and $R^{11}OC(O)$-NR^{10}-;or two R^{1c}s on the same carbon are combined with that carbon to form a C_4-C_6 cycloalkyl;

R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,

wherein the substituted group is substituted with one or more of:
         1)   aryl or heterocycle, unsubstituted or substituted with:
              a) C_{1-4} alkyl,

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b) $(CH_2)_pOR^6$,

c) $(CH_2)_pNR^6R^7$,

d) halogen,

e) CN,

f) aryl or heteroaryl,

g) perfluoro-C_{1-4} alkyl,

h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},

2) C_{3-6} cycloalkyl,

3) OR^6,

4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},

5) $—NR^6R^7$,

6) ,

7) ,

8) ,

9) ,

10) ,

11) $—SO_2—NR^6R^7$,

12) ,

13)

,

14)

,

15) N_3,

16)   F,   or

17)   perfluoro-C_{1-4}-alkyl; or
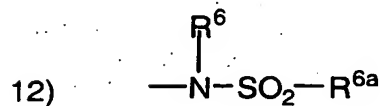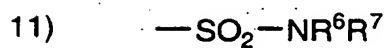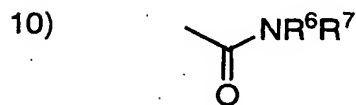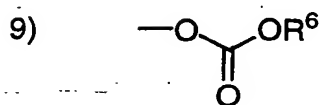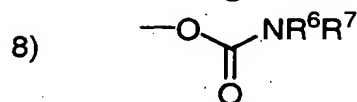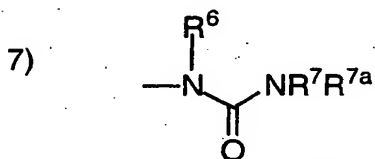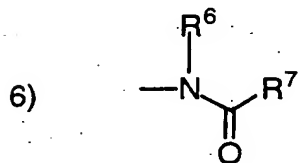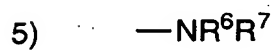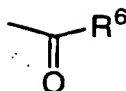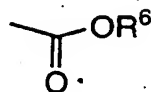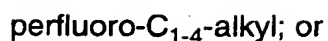
R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$- wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -N(COR^{10})-;

R^4 is selected from H and CH_3; and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

    a) C_{1-4} alkoxy,

    b) aryl or heterocycle,

    c) halogen,

    d) HO,

    e)   ,

    f)   —SO_2R^{11} , or

    g) N(R^{10})$_2$; or

R^6 and R^7 may be joined in a ring;

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R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl,

unsubstituted or substituted with:

    a) C_{1-4} alkoxy,

    b) aryl or heterocycle,

    c) halogen,

    d) HO,

    e)

    ,

    f) $-SO_2R^{11}$, or

    g) $N(R^{10})_2$;

R^8 is independently selected from:

    a) hydrogen,

    b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

    c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

    a) hydrogen,

b)   alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$-, or S(O)$_m$;

A^3 is selected from: -C(O)-, -C(O)NR^{10}-, -C(O)O-, S(O)$_m$ or a bond;

A^4 is selected from: bond, -O- and -NR^{10}-;

G is H_2 or O, provided that G is not H_2, if A^3 is a bond;

V is selected from:
a)   hydrogen,
b)   heterocycle,
c)   aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

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e) C_2-C_{20} alkenyl, provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

5   W is a heterocycle;

Z is an unsubstituted or substituted multicyclic ring, wherein the substituted multicyclic ring is substituted with one or two moieties selected from the following:

10   a) C_{1-4} alkoxy,

b) NR^6R^7,

c) C_{3-6} cycloalkyl,

d) -$NR^6C(O)R^7$,

e) HO,

15   f) -$S(O)_mR^{6a}$,

g) halogen,

h) perfluoroalkyl, and

i) C_{1-4} alkyl;

20   m is   0, 1 or 2;

n is   0, 1, 2, 3 or 4;

p is   0, 1, 2, 3 or 4;

q is   1 or 2;

r is   0 to 5, provided that r is 0 when V is hydrogen;

25   s is   0 or 1;

t is   0 or 1;

u is   4 or 5; and

v is   0, 1, 2 or 3;

30   or the pharmaceutically acceptable salts thereof.

In a preferred embodiment of this invention, the inhibitors of prenyl-protein transferase are illustrated by the formula A:

-13-

$$V - A^1(CR^{1a}_2)_nA^2(CR^{1a}_2)_n - \left(\overset{(R^9)_q}{\underset{t}{W}}\right) - (CR^{1b}_2)_p - N \underset{R^3 \quad R^4}{\overset{R^2 \qquad G}{\underset{(_s}{\bigcirc}}} N - A^3(CR^{1c}_2)_v A^4 Z$$

$(R^8)_r$ is attached to $V - A^1$.

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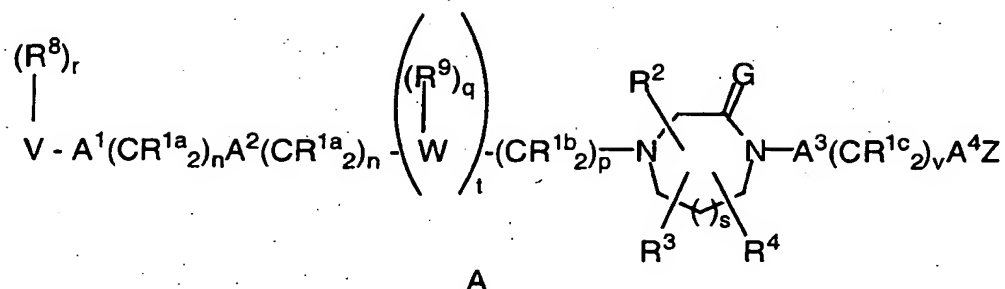
wherein:

5   R^{1a} is independently selected from: hydrogen or C_1-C_6 alkyl;
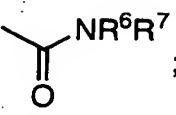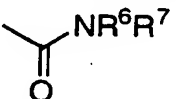
R^{1b} is independently selected from:
- a)   hydrogen,
- b)   aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6
10   alkenyl,
- c)   unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

15

R^{1c} is independently selected from:
- a)   hydrogen,
- b) $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,
20   c)   unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$ and $R^{11}OC(O)$-NR^{10}-;or two R^{1c}s on the same carbon are combined
25   with that carbon to form a C_4-C_6 cycloalkyl;

R^3 and R^4 are independently selected from H and CH_3;

R^2 is   H; [structure: NR^6R^7 attached to C=O] ; or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1)   aryl,

2)   heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{6a}, or

5)   [structure: NR^6R^7 attached to C=O] ;

and any two of R^2, R^3, R^4, and R^5 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b)   halogen, or

c)   aryl or heterocycle;

R^{6a} is selected from: C_{1-4} alkyl or C_{3-6} cycloalkyl,   unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b)   halogen, or

c)   aryl or heterocycle;

R^8 is independently selected from:

a)   hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or S(O)$_m$;

A^3 is selected from: -C(O)-, -C(O)NR^{10}-, -C(O)O-, S(O)$_m$ or a bond;

A^4 is selected from: bond, -O- and -NR^{10}-;

G is H_2 or O, provided that G is not H_2, if A^3 is a bond;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

    d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

    e) C_2-C_{20} alkenyl, and provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring, wherein the substituted C_7-C_{10} multicyclic alkyl ring is substituted with one or two moieties selected from the following:

    a) C_{1-4} alkoxy,

    b) NR^6R^7,

    c) C_{3-6} cycloalkyl,

    d)   -$NR^6C(O)R^7$,

    e)   HO,

    f)   -$S(O)_mR^{6a}$,

    g)   halogen,

    h)   perfluoroalkyl, and

    i) C_{1-4} alkyl;

m is	0, 1 or 2;
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
r is	0 to 5, provided that r is 0 when V is hydrogen;
s is	0 or 1;
t is	0 or 1; and
v is	0, 1, 2 or 3; provided that v is not 0 if A^3 is a bond;

or the pharmaceutically acceptable salts thereof.

A preferred embodiment of the compounds of this invention are illustrated by the formula B:

$$V - A^1(CR^{1a}_2)_nA^2(CR^{1a}_2)_n-N \quad \overset{R^{9a}}{\underset{(CR^{1b}_2)_p}{\bigvee}} \quad \overset{R^2}{\underset{R^3}{\bigvee}} N-A^3(CR^{1c}_2)_vA^4Z$$

$$(R^8)_r$$

B

wherein:

5

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl,

10 c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;
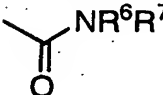
R^{1c} is independently selected from:

a) hydrogen,

15 b) $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-

20 $C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$ and $R^{11}OC(O)$-NR^{10}-;or two R^{1c}s on the same carbon are combined with that carbon to form a C_4-C_6 cycloalkyl;

R^3 is selected from H and CH_3;

25 R^2 is selected from H; $\underset{O}{\overset{NR^6R^7}{\bigvee}}$; or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

-18-

1)   aryl,

2)   heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{6a}, or

5) NR^6R^7 ;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

     a) C_{1-4} alkoxy,

     b)   halogen, or

     c)   aryl or heterocycle;

R^{6a} is selected from: C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

     a) C_{1-4} alkoxy,

     b)   halogen, or

     c)   aryl or heterocycle;

R^8 is independently selected from:

     a)   hydrogen,

     b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

     c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

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R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-,
-C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or S(O)$_m$;

A^3 is selected from: -C(O)-, -C(O)NR^{10}-, -C(O)O- or S(O)$_m$;

A^4 is selected from: bond, -O- and -NR^{10}-;

V is selected from:
  a)   hydrogen,
  b)   heterocycle selected from pyrrolidinyl, imidazolyl,
        pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl,
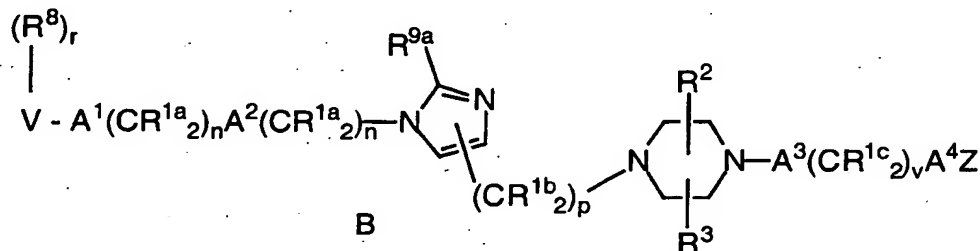   indolyl, quinolinyl, isoquinolinyl, and thienyl,
  c)   aryl,
  d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are
        replaced with a a heteroatom selected from O, S, and
        N, and
  e) C_2-C_{20} alkenyl, and provided that V is not hydrogen if
        A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is
        0 and A^2 is S(O)$_m$;

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring,
wherein the substituted C_7-C_{10} multicyclic alkyl ring is
substituted with one or two moieties selected from the following:
  a) C_{1-4} alkoxy,
  b) NR^{6}R^7,
  c) C_{3-6} cycloalkyl,
  d) -NR^{6}C(O)R^7,
  e) HO,
  f) -S(O)$_m$R^{6a},
  g) halogen,
  h) perfluoroalkyl, and

-20-

i) C_{1-4} alkyl;

C_7-C_{10} multicyclic alkyl ring is selected from:

5   m is   0, 1 or 2;

n is   0, 1, 2, 3 or 4;

p is   0, 1, 2, 3 or 4;

r is   0 to 5, provided that r is 0 when V is hydrogen; and

v is   0, 1, 2 or 3; provided that v is not 0 if A^3 is a bond;

10

or the pharmaceutically acceptable salts thereof.

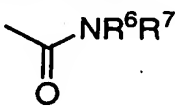Another preferred embodiment of the compounds of this invention are illustrated by the formula C:

15

wherein:

R^{1a} and R^{1b} are independently selected from:

a)   hydrogen,

b)   aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^{1c} is independently selected from:

a)   hydrogen,

b) $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,

c)   unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ and $R^{11}OC(O)$-NR^{10}-;or two R^{1c}s on the same carbon are combined with that carbon to form a C_4-C_6 cycloalkyl;

R^3 is selected from H and CH_3;

R^2 is selected from   H;   [structure: $\overset{\displaystyle NR^6R^7}{\underset{\displaystyle O}{\diagup}}$] ;   or $C_{1\text{-}5}$ alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1)   aryl,

2)   heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{6a}, or

5)   [structure: $\overset{\displaystyle NR^6R^7}{\underset{\displaystyle O}{\diagup}}$] ;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; $C_{1\text{-}4}$ alkyl, $C_{3\text{-}6}$ cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

-22-

    a) C_{1-4} alkoxy,

    b)   halogen, or

    c)   aryl or heterocycle;

5   R^{6a} is selected from: C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

    a) C_{1-4} alkoxy,

    b)   halogen, or

    c)   aryl or heterocycle;

10

R^8 is independently selected from:

    a)   hydrogen,

    b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

    c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

20

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

25

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or S(O)_m;

30

A^3 is selected from: -C(O)-, -C(O)NR^{10}-, -C(O)O- or S(O)_m;

A^4 is selected from: bond, -O- and -NR^{10}-;

V is selected from:
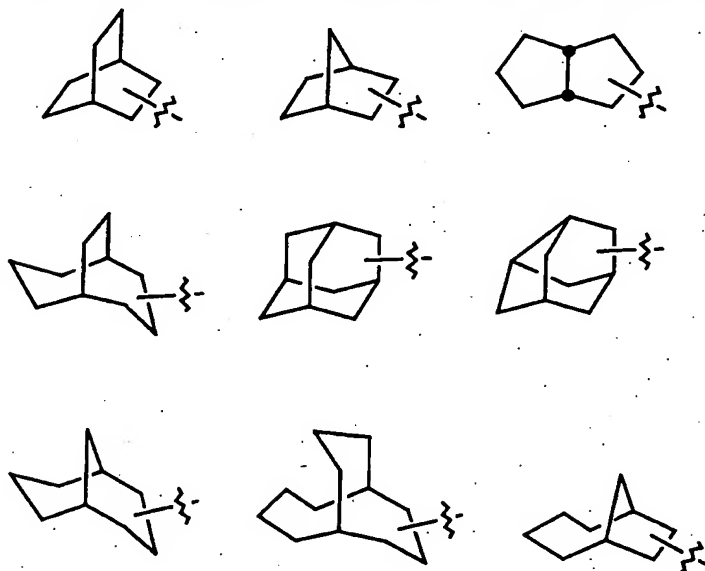
    a)   hydrogen,

    b)   heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

    c)   aryl,

    d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

    e) C_2-C_{20} alkenyl, and provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring, wherein the substituted C_7-C_{10} multicyclic alkyl ring is substituted with one or two moieties selected from the following:

    a) C_{1-4} alkoxy,

    b) NR^6R^7,

    c) C_{3-6} cycloalkyl,

    d) -$NR^6C(O)R^7$,

    e) HO,

    f) -$S(O)_mR^{6a}$,

    g) halogen,

    h) perfluoroalkyl, and

    i) C_{1-4} alkyl;

C_7-C_{10} multicyclic alkyl ring is selected from:

m is	0, 1 or 2;
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
r is	0 to 5, provided that r is 0 when V is hydrogen; and
v is	0, 1, 2 or 3; provided that v is not 0 if A^3 is a bond;

or the pharmaceutically acceptable salts thereof.

A further embodiment of the compounds of this invention is illustrated by the formula D:

D

wherein:

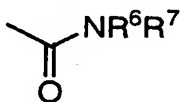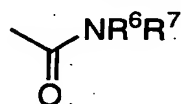R^{1a} and R^{1b} are independently selected from:

   a) hydrogen,

-25-

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^{1c} is independently selected from:

a) hydrogen,

b) $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ and $R^{11}OC(O)$-NR^{10}-;

R^3 is selected from H and CH_3;

R^2 is selected from H; $\underset{O}{\overset{NR^6R^7}{\bigvee}}$; or $C_{1\text{-}5}$ alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,

2) heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{6a}, or

5) $\underset{O}{\overset{NR^6R^7}{\bigvee}}$;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; $C_{1\text{-}4}$ alkyl, $C_{3\text{-}6}$ cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) $C_{1\text{-}4}$ alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^{6a} is selected from:　C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

    a)　　C_{1-4} alkoxy,

    b)　　halogen, or

    c)　　aryl or heterocycle;

R^8 is independently selected from:

    a)　　hydrogen,

    b)　　C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

    c)　　C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 is selected from:　a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or $S(O)_m$;

A^3 is selected from: -C(O)-, -C(O)NR^{10}- or -C(O)O-;

A^4 is selected from: bond and -O-;

V is selected from:

    a)　　heterocycle selected from pyridinyl and quinolinyl, and

    b)　　aryl;

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring, wherein the substituted C_7-C_{10} multicyclic alkyl ring is substituted with one or two moieties selected from the following:

5
- a) C_{1-4} alkoxy,
- b) NR^6R^7,
- c) C_{3-6} cycloalkyl,
- d) -$NR^6C(O)R^7$,
- e) HO,

10
- f) -$S(O)_mR^{6a}$,
- g) halogen,
- h) perfluoroalkyl, and
- i) C_{1-4} alkyl;

15   C_7-C_{10} multicyclic alkyl ring is selected from:
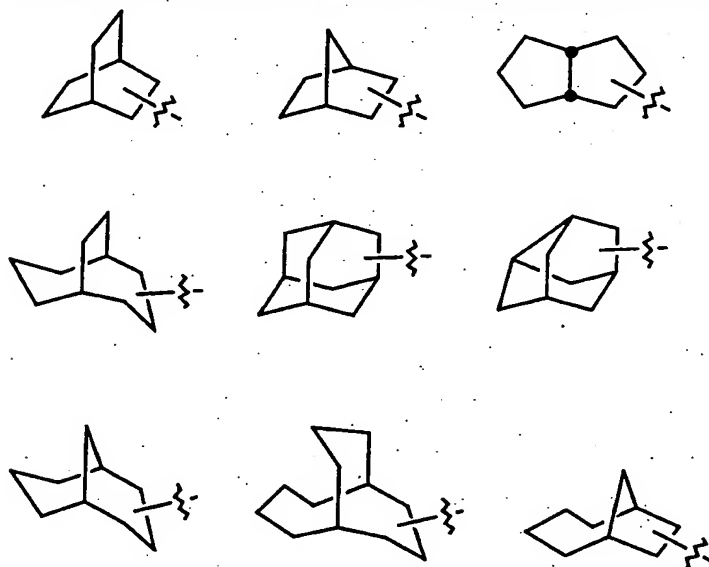
m is   0, 1 or 2;

n is   0, 1, 2, 3 or 4;

20 p is   0, 1, 2, 3 or 4;

r is   0 to 5, and

v is   0, 1, 2 or 3;

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or the pharmaceutically acceptable salts thereof.

Another embodiment of the compounds of this
5   invention is illustrated by the formula E:

E

wherein:

R^{1a} and R^{1b} are independently selected from:
10   a)   hydrogen,
        b)   aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6
                alkenyl,
        c) C_1-C_6 alkyl unsubstituted or substituted by aryl,
                heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

15
R^{1c} is independently selected from:
        a)   hydrogen,
        b) $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-,
                CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,
20   c)   unsubstituted or substituted C_1-C_6 alkyl wherein the
                substitutent on the substituted C_1-C_6 alkyl is selected
                from $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-
                $C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ and $R^{11}OC(O)$-
                NR^{10}-;

25
R^3 is selected from H and CH_3;

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R^2 is selected from   H; $\overset{\displaystyle NR^6R^7}{\underset{O}{\diagup}}$;   or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1)   aryl,
2)   heterocycle,
3) OR^6,
4) SR^{6a}, SO_2R^{6a}, or
5) $\overset{\displaystyle NR^6R^7}{\underset{O}{\diagup}}$;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b)   halogen, or
c)   aryl or heterocycle;

R^{6a} is selected from: C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b)   halogen, or
c)   aryl or heterocycle;

R^8 is independently selected from:

a)   hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

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R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl

5   and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 is selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O,

10   -N(R^{10})-, or S(O)$_m$;

A^3 is selected from: -C(O)-, -C(O)NR^{10}- or -C(O)O-;

A^4 is selected from: bond and -O-;

15

V is selected from:

      a)   heterocycle selected from pyridinyl and quinolinyl, and

      b)   aryl;

20

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring, wherein the substituted C_7-C_{10} multicyclic alkyl ring is substituted with one or two moieties selected from the following:

      a) C_{1-4} alkoxy,

25   b)   NR^{6}R^7,

      c) C_{3-6} cycloalkyl,

      d)   -NR^{6}C(O)R^7,

      e)   HO,

      f)   -S(O)$_m$R^{6a},

30   g)   halogen,

      h)   perfluoroalkyl, and
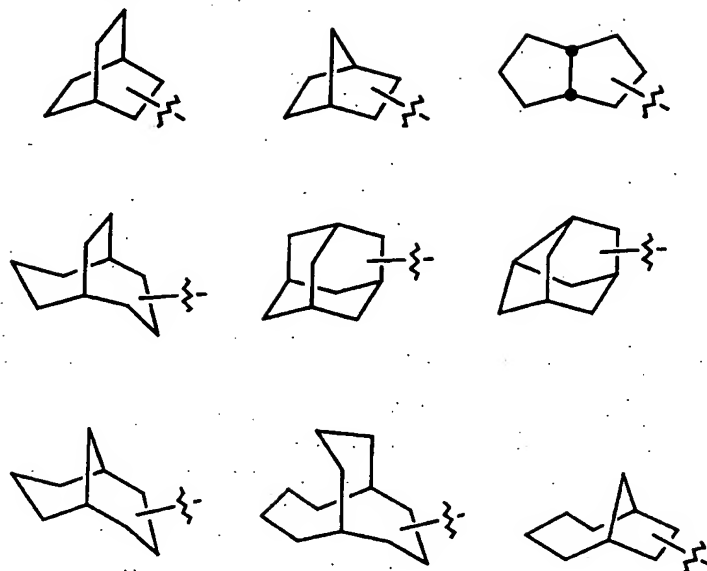
      i) C_{1-4} alkyl;

C_7-C_{10} multicyclic alkyl ring is selected from:

m is   0, 1 or 2;
n is   0, 1, 2, 3 or 4;
p is   0, 1, 2, 3 or 4;
r is   0 to 5, and
v is   0, 1, 2 or 3;

or the pharmaceutically acceptable salts thereof.

A still further embodiment of the compounds of this invention is illustrated by the formula F:

F

wherein:

R^{1b} is independently selected from:

    a)   hydrogen,

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　b)　　aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,

　c)　　C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^{1c} is independently selected from:

　a)　　hydrogen,

　b)　　$R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,

　c)　　unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ and $R^{11}OC(O)$-NR^{10}-;

R^3 is selected from H and CH_3;

R^2 is selected from　　　H;　 　　 　or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

　1)　　aryl,

　2)　　heterocycle,

　3)　　OR^6,

　4)　　SR^{6a}, SO_2R^{6a}, or

　5)

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from:　H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

　a)　　C_{1-4} alkoxy,

　b)　　halogen, or

　c)　　aryl or heterocycle;

R^{6a} is selected from: C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

    a) C_{1-4} alkoxy,

    b)   halogen, or

    c)   aryl or heterocycle;

R^8 is independently selected from:

    a)   hydrogen,

    b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

    c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^3 is selected from: -C(O)-, -C(O)NR^{10}- or -C(O)O-;

A^4 is selected from: bond and -O-;

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring, wherein the substituted C_7-C_{10} multicyclic alkyl ring is substituted with one or two moieties selected from the following:

    a) C_{1-4} alkoxy,

    b) NR^6R^7,

    c) C_{3-6} cycloalkyl,

    d) -$NR^6C(O)R^7$,

e) HO,

f) $-S(O)_m R^{6a}$,

g) halogen,

h) perfluoroalkyl, and

i) C_{1-4} alkyl;

C_7-C_{10} multicyclic alkyl ring is selected from:

m is	0, 1 or 2;
p is	1, 2 or 3;
r is	0 to 5, and
v is	0, 1, 2 or 3;

or the pharmaceutically acceptable salts thereof.

Another further embodiment of the compounds of this invention is illustrated by the formula G:
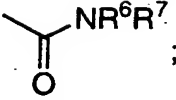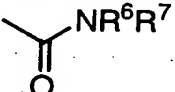

G

wherein:

R^{1b} is independently selected from:

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a)   hydrogen,

b)   aryl, heterocycle, cycloalkyl, $R^{10}O\text{-}$, $-N(R^{10})_2$ or $C_2\text{-}C_6$ alkenyl,

c) $C_1\text{-}C_6$ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O\text{-}$, or $-N(R^{10})_2$;

R^{1c} is independently selected from:

a)   hydrogen,

b) $R^{10}O\text{-}$, $R^{10}C(O)NR^{10}\text{-}$, $(R^{10})_2NC(O)\text{-}$, $R^{10}{}_2N\text{-}C(NR^{10})\text{-}$, CN, NO_2, $R^{10}C(O)\text{-}$, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}\text{-}$,

c)   unsubstituted or substituted $C_1\text{-}C_6$ alkyl wherein the substitutent on the substituted $C_1\text{-}C_6$ alkyl is selected from $R^{10}O\text{-}$, $R^{10}C(O)NR^{10}\text{-}$, $(R^{10})_2NC(O)\text{-}$, $R^{10}{}_2N\text{-}C(NR^{10})\text{-}$, CN, $R^{10}C(O)\text{-}$, N_3, $-N(R^{10})_2$ and $R^{11}OC(O)\text{-}NR^{10}\text{-}$;

R^3 is selected from H and CH_3;

R^2 is selected from   H;   [structure: \\/\NR^{6}R^7 with C=O] ;   or $C_{1\text{-}5}$ alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1)   aryl,

2)   heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{6a}, or

5)   [structure: \\/\NR^{6}R^7 with C=O] ;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; $C_{1\text{-}4}$ alkyl, $C_{3\text{-}6}$ cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) $C_{1\text{-}4}$ alkoxy,

b)   halogen, or

c)   aryl or heterocycle;

R^{6a} is selected from: C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

      a) C_{1-4} alkoxy,

5   b)   halogen, or

      c)   aryl or heterocycle;

R^8 is independently selected from:

      a)   hydrogen,

10   b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

      c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl,

15            $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

20   R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

25   A^3 is selected from: -$C(O)$-, -$C(O)NR^{10}$- or -$C(O)O$-;

A^4 is selected from: bond and -O-;

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring,

30   wherein the substituted C_7-C_{10} multicyclic alkyl ring is substituted with one or two moieties selected from the following:

      a) C_{1-4} alkoxy,

      b) NR^6R^7,

      c) C_{3-6} cycloalkyl,

d) -NR^{6}C(O)R^7,

e) HO,

f) -S(O)$_m$R^{6a},

g) halogen,

5   h) perfluoroalkyl, and

i) C$_{1-4}$ alkyl;

C$_7$-C$_{10}$ multicyclic alkyl ring is selected from:

10

m is   0, 1 or 2;

p is   1, 2 or 3;

r is   0 to 5, and

v is   0, 1, 2 or 3;

15

or the pharmaceutically acceptable salts thereof.

Specific examples of compounds of this invention are as follows:

20

1-(4-Cyanobenzyl)-5-[1-(2-oxo-2-(adamant-1-yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole

R/S 1-(4-Cyanobenzyl)-5-[1-(2-hydroxy-2-(adamant-1-yl)ethyl)-2-

25   oxo-piperazin-4-yl-methyl]imidazole

1-(4-Cyanobenzyl)-5-[1-(2-hydroxy-2-(adamant-1-yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole

1-(4-Cyanobenzyl)-5-[1-(2-acetyloxy-2-(adamant-1-yl)ethyl)-2-oxo-
piperazin-4-yl-methyl]imidazole

5   1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl] piperazine-4-(N-1-
adamantyl)carboxamide

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-(N-1-
adamantyl)carbonyl piperazine

10

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-[N-(1R)-(-)-10-
camphorsulfonyl]piperazine

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-(1-adamantylmethyl)
15   piperazine

1-(4-Cyanobenzyl)-5-[1-(2-(adamant-1-yl)ethyl)-2-oxo-piperazin-4-
yl-methyl]imidazole

20   1-(4-Cyanobenzyl)-5-[1-(1-(adamant-1-yl)methyl)-2-oxo-piperazin-4-
yl-methyl]imidazole

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl] piperazine-4-carboxylic
acid (2-norbornane)methyl ester

25

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-piperazine-4-carboxylic
acid (2-norbornane)methyl ester

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl] -4-(2-bicyclo-[2.2.2]-
30   octylcarbonyl)piperazine

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-(2-
norbornanecarbonyl)piperazine

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-cis/trans-(2,6,6-trimethylbicyclo[3.1.1]heptanecarbonyl)-piperazine

1-(4'-Cyanobenzyl)-2-methyl-imidazol-5-ylmethyl piperazine-4-(N-1-
adamantyl)carboxamide

or the pharmaceutically acceptable salts or optical isomers thereof.

The compounds of the instant invention differ from previously disclosed piperazinone-containing and piperazine-containing compounds, (PCT Publ. No. WO 96/30343 - October 3, 1996; U.S. Pat. No. 5,856,326 - January 5, 1999; PCT Publ. No. WO 96/31501 - October 10, 1996; PCT Publ. No. WO 97/36593 - October 9, 1997; PCT Publ. No. WO 97/36592 - October 9, 1997) that were described as inhibitors of farnesyl-protein transferase (FPTase), in that, among other things, the instant compounds are dual inhibitors of farnesyl-protein transferase and geranylgeranyl-protein transferase type I (GGTase-I).

In one embodiment of the invention, the compounds are further characterized in that the inhibitory activity of the compounds against GGTase-I is greater than the inhibitory activity against FPTase. Preferably, the compounds of this embodiment of the instant invention inhibit FPTase in vitro (Example 16) at an IC_{50} of less than 1 μM and inhibit GGTase-I in vitro (Example 17) at an IC_{50} of less than 50 nM. Also preferably, the compounds of this embodiment of the instant invention inhibit the cellular processing of the Rap1 protein (Example 22, Protocol C) at an EC_{50} of less than about 1 μM. More preferably, the compounds of this embodiment of the instant invention inhibit the cellular processing of the Rap1 protein (Example 22, Protocol C) at an EC_{50} of less than about 50 nM. Also more preferably, the ratio of the IC_{50} of the compounds of this embodiment of the instant invention for in vitro inhibition of FPTase to the IC_{50} of the compounds of the instant invention for

in vitro inhibition of GGTase type I is greater than 25. Also more preferably, the ratio of the EC_{50} of the compounds of this embodiment of the instant invention for inhibition of the cellular processing of the hDJ protein (Example 21) to the EC_{50} of the

5   compounds of the instant invention for inhibition of the cellular processing of the Rap1 protein is about equal to or less than 1.

In a second embodiment of the compounds of the instant invention, the compounds are further characterized in that the inhibitory activity of the compounds against FPTase is

10   greater than the inhibitory activity against GGTase-I. Preferably, the compounds of this second embodiment of the instant invention inhibit FPTase in vitro (Example 16) at an IC_{50} of less than 100 nM and inhibit GGTase-I in vitro (Example 17) at an IC_{50} of less than 5 μM. Preferably, the compounds of this second

15   embodiment of the instant invention inhibit the cellular processing of the hDJ protein (Example 21) at an EC_{50} of less than about 250 nM. Also preferably, the compounds of this second embodiment of the instant invention inhibit the cellular processing of the Rap1 protein (Example 22, Protocol C) at an

20   EC_{50} of less than about 10 μM. More preferably, the compounds of this second embodiment of the instant invention inhibit the cellular processing of the Rap1 protein (Example 22, Protocol C) at an EC_{50} of less than about 1 μM. Also more preferably, the ratio of the IC_{50} of the compounds of this embodiment of the

25   instant invention for in vitro inhibition of GGTase type I to the IC_{50} of the compounds of the instant invention for in vitro inhibition of FPTase is greater than 1 and less than 25. Also more preferably, the ratio of the EC_{50} of the compounds of this second embodiment of the instant invention for inhibition of the cellular

30   processing of the hDJ protein (Example 21) to the EC_{50} of the compounds of the instant invention for inhibition of the cellular processing of the Rap1 protein is between about 1 and about 100.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures,

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and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. When any variable (e.g. aryl, heterocycle, R^1, R^2 etc.) occurs more than one time in any constituent, its definition on

5   each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon

10   groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "cycloalkyl" is intended to include

15   monocyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Examples of such cycloalkyl groups includes, but are not limited to, cyclopropyl, cyclobutyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein, "aryl" is intended to mean any stable

20   monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein,

25   represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-

30   defined heterocyclic rings is fused to a benzene ring. The term heterocycle or heterocyclic, as used herein, includes heteroaryl moieties. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include,

but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl,

5   dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-

10   oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl,

15   thienofuryl, thienothienyl, and thienyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected

20   from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimid-azolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzo-thiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl,

25   dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydro-benzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl,

30   quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, and thienyl.

As used herein in the definition of R^2 and R^3, the term "the substituted group" intended to mean a substituted C_{1-8} alkyl, substituted C_{2-8} alkenyl, substituted C_{2-8} alkynyl, substituted

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aryl or substituted heterocycle from which the substituent(s) R^2 and R^3 are selected.

As used herein in the definition of R^6, R^{6a}, R^7 and R^{7a}, the substituted C_{1-8} alkyl, substituted C_{3-6} cycloalkyl,

5   substituted aroyl, substituted aryl, substituted heteroaroyl, substituted arylsulfonyl, substituted heteroarylsulfonyl and substituted heterocycle include moieties containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound. Preferably, such substituents are selected from

10   the group which includes but is not limited to F, Cl, Br, CF3, NH_2, $N(C_1-C_6$ alkyl$)_2$, NO_2, CN, $(C_1-C_6$ alkyl$)O$-, -OH, $(C_1-C_6$ alkyl$)S(O)_m$-, $(C_1-C_6$ alkyl$)C(O)NH$-, $H_2N-C(NH)$-, $(C_1-C_6$ alkyl$)C(O)$-, $(C_1-C_6$ alkyl$)OC(O)$-, N_3,$(C_1-C_6$ alkyl$)OC(O)NH$-, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl,

15   furyl, isothiazolyl and C_1-C_{20} alkyl.

As used herein, " multicyclic ring" is intended to include polycyclic saturated and unsaturated aliphatic hydrocarbon groups which optionally contain 1-3 heteroatoms, selected from N, O and S.

Examples of such multicyclic rings includes, but are not limited to:
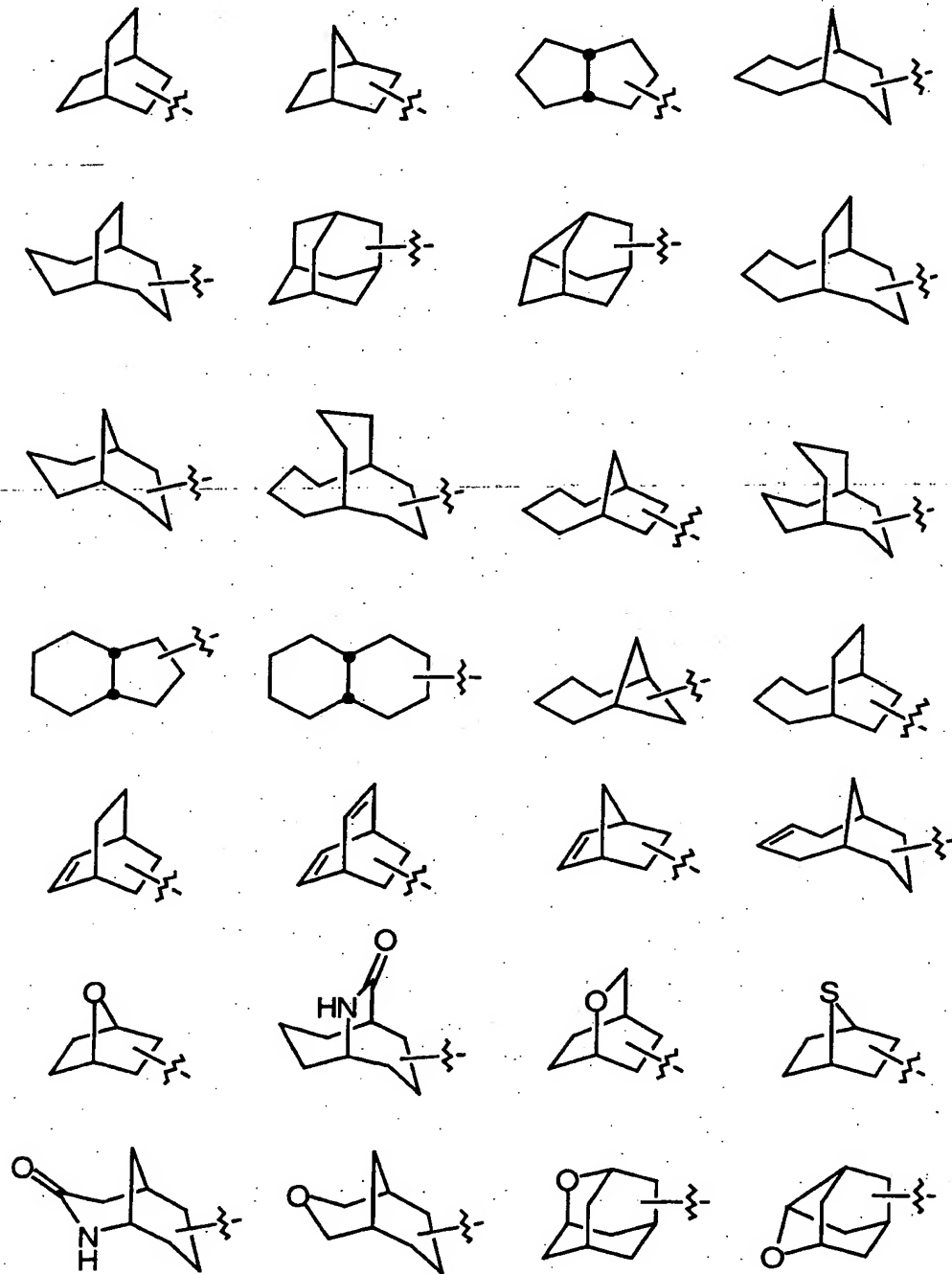
As used herein, "multicyclic alkyl ring" is intended to include polycyclic saturated and unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Examples of such cycloalkyl groups includes, but are not

5   limited to:

When R^2 and R^3 are combined to form - $(CH_2)_u$ -, and when two R^{1c}s on the same carbon are combined with that carbon to form a C_4-C_6 cycloalkyl, cyclic moieties are formed.

10   Examples of such cyclic moieties include, but are not limited to:
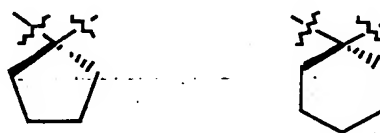
In addition, with respect to R^2 and R^3, such cyclic moieties may optionally include a heteroatom(s). Examples of

15   such heteroatom-containing cyclic moieties include, but are not limited to:
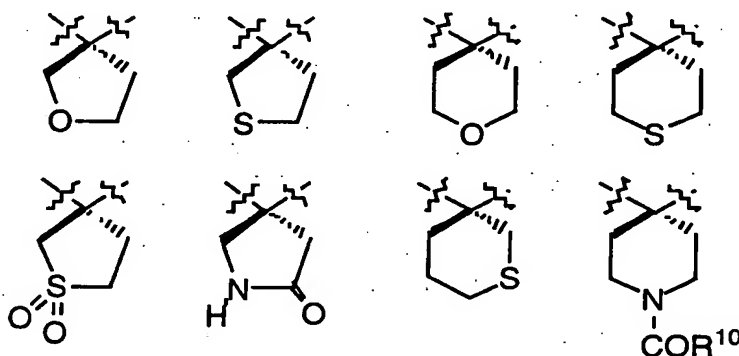
The moiety formed when, in the definition of R^6, R^7

20   and R^{7a}, R^6 and R^7 or R^7 and R^{7a} are joined to form a ring, is illustrated by, but not limited to, the following:
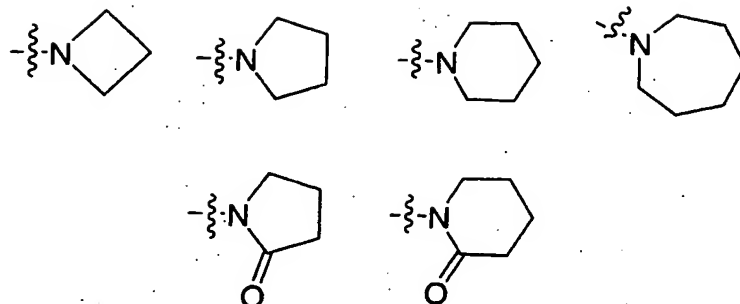
Lines drawn into the ring systems from substituents (such as from R^2, R^3, R^4 etc.) represent that the indicated bond may be attached to any of the substitutable ring carbon atoms.

5   Preferably, R^{1a} and R^{1b} are independently selected from: hydrogen, $-N(R^{10})_2$, $R^{10}C(O)NR^{10}-$ or unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted phenyl, $-N(R^{10})_2$, $R^{10}O-$ and $R^{10}C(O)NR^{10}-$.

10   Preferably, R^2 is selected from: hydrogen,
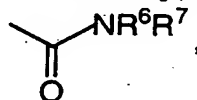
and an unsubstituted or substituted group, the group selected from C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkynyl; wherein the substituted group is substituted with one or more of:

15   1)   aryl or heterocycle,
             2) OR^6, and
             3) SR^{6a}, SO_2R^{6a}.

Preferably, R^3 is selected from hydrogen and methyl.
20   Preferably, R^4 is hydrogen.
     Preferably, R^6 and R^7 are selected from: hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl and unsubstituted or substituted C_3-C_6 cycloalkyl.
25   Preferably, R^{6a} is unsubstituted or substituted C_1-C_6.
     Preferably, R^9 is hydrogen or methyl.

Preferably, R^{10} is selected from H, C_1-C_6 alkyl and benzyl.

Preferably, A^1 and A^2 are independently selected from: a bond, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})-
5   and -N(R^{10})S(O)$_2$-. Most preferably, A^1 and A^2 are a bond.

Preferably, A^3 is selected from: -C(O)-, -C(O)NR^{10}- and -C(O)O-.

Preferably, A^4 is a bond.

Preferably, V is selected from heteroaryl and aryl.
10   More preferably, V is phenyl.

Preferably, W is selected from imidazolyl, pyridinyl, thiazolyl, indolyl, quinolinyl, or isoquinolinyl. More preferably, W is imidazolyl and pyridyl.

Preferably, Z is a unsubstituted or substituted C_7-C_{10}
15   multicyclic alkyl ring.

Preferably, the C_7-C_{10} multicyclic alkyl ring is selected from:
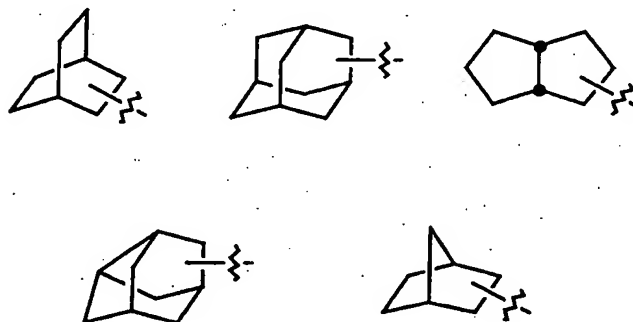
Preferably, n and r are independently 0, 1, or 2.
20   Preferably p is 1, 2 or 3.

Preferably s is 0.

Preferably t is 1.

Preferably v is 0, 1 or 2.

Preferably, the moiety

$$V - A^1(CR^{1a}_2)_n A^2(CR^{1a}_2)_n \left(W \overset{(R^9)_q}{} \right)_t - (CR^{1b}_2)_p$$

is selected from:

and
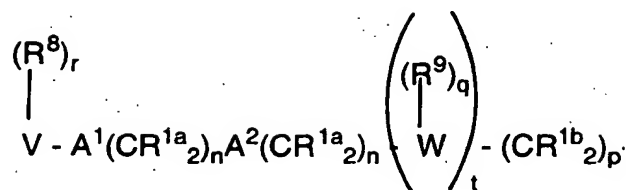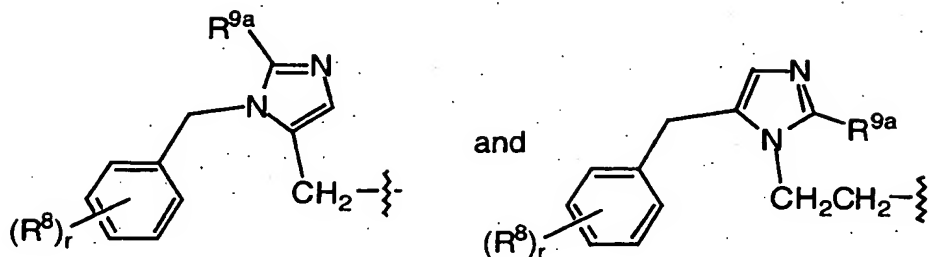
Preferably, the moiety $A^1(CR^{1a}_2)_n A^2(CR^{1a}_2)_n$ is not a bond.

It is intended that the definition of any substituent or variable (e.g., R^{1a}, R^9, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus,-$N(R^{10})_2$ represents -NHH, -NHCH3, -NHC2H5, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric,

citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

5   The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange chromatography or by reacting the free

10   base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the

15   Schemes 1-21, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R, R^a and R^b, as shown in the Schemes, represent the substituents R^2, R^3 and R^4; however their point of

20   attachment to the ring is illustrative only and is not meant to be limiting. Substituent Z', as shown in the Schemes, represents the substiutent Z as defined hereinabove or a protected precursor thereof.

These reactions may be employed in a linear sequence

25   to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

Synopsis of Schemes 1-21:

30   The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. In Scheme 1, for example, the synthesis of 2-cycloalkylalkanoyl substituted piperazines is outlined. Boc-protected amino acids I, available

-50-

commercially or by procedures known to those skilled in the art, can be coupled to N-benzyl amino acid esters using a variety of dehydrating agents such as DCC (dicyclohexycarbodiimide) or EDC·HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

5   hydrochloride) in a solvent such as methylene chloride, chloroform, dichloroethane, or dimethylformamide. The product II is then deprotected with acid, for example hydrogen chloride in chloroform or ethyl acetate, or trifluoroacetic acid in methylene chloride, and cyclized under weakly basic conditions to give the

10   diketopiperazine III. Reduction of III with lithium aluminum hydride in refluxing ether gives the piperazine IV, which is protected as the Boc derivative V. The N-benzyl group can be cleaved under standard conditions of hydrogenation, e.g., 10% palladium on carbon at 60 psi hydrogen on a Parr apparatus for

15   24-48 h. The product VI can be reacted with a suitably substituted carboxylic acid to provide the piperazine VII; a final acid deprotection as previously described gives the intermediate VIII (Scheme 2). The intermediate VIII can itself be reductively alkylated with a variety of aldehydes, such as IX. The aldehydes

20   can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, 1988, 67, 69-75, from the appropriate amino acid (Scheme 3). The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium

25   triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The product X can be deprotected to give the final compounds XI with trifluoroacetic acid in methylene chloride. The final product XI is isolated in the salt form, for example, as a trifluoroacetate,

30   hydrochloride or acetate salt, among others. The product diamine XI can further be selectively protected to obtain XII, which can subsequently be reductively alkylated with a second aldehyde to obtain XIII. Removal of the protecting group, and

conversion to cyclized products such as the dihydroimidazole XV can be accomplished by literature procedures.

As shown in Scheme 4, the piperazine intermediate VIII can be reductively alkylated with other aldehydes such as 1-

5   trityl-4-imidazolyl-carboxaldehyde or 1-trityl-4-imidazolyl-acetaldehyde, to give products such as XVI. The trityl protecting group can be removed from XVI to give XVII, or alternatively, XVI can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole XVIII. Alternatively,

10   the intermediate VIII can be acylated or sulfonylated by standard techniques.

Incorporation of a hydroxyl moiety on the sidechain carbon alpha to the amide carbonyl of compounds of the formula XVIII can be accomplished as illustrated in Scheme 5. A suitably

15   substituted primary alcohol XIX undergoes a one carbon homologation, via a Swern oxidation, nitrile addition and hydrolysis, to provide the substituted hydroxyacetic acid XX. The trifluoromethyl ketal is formed and reacted with the previously described protected piperazine VI to provide,

20   following deprotection, the intermediate XXI. Intermediate XXI can undergo a variety of reactions at its unsubstituted nitrogen. For example, treatment of XXI with a suitably substituted imidazolylmethyl halide to provide the instant compound XXII.

Scheme 6 illustrates incorporation of a

25   cycloalkylalkoxycarbonyl moiety onto the piperazine nitrogen. Thus a suitably substituted alcohol XXIII is reacted with nitrophenylchloroformate to provide the intermediate XXIV, which is reacted with a suitably substituted piperazine to provide the instant compound XXV. An analogous reaction sequence

30   alternatively provides the corresponding aminocarbonyl substitution on the piperazine nitrogen, as shown in Scheme 7.

Scheme 8 illustrates the preparation of compounds analogous to compound XXXI wherein the alcohol utilized in the first step is a suitably substituted adamantanol. The scheme also

illustrates the incorporation of an indole moiety for the
substiutent W in place of the preferred benzylimidazolyl moiety.

Scheme 9 illustrates synthesis of an instant
compound wherein a non-hydrogen R^{9b} is incorporated in the
5   instant compound. Thus, a readily available 4-substituted
imidazole XXVI may be selectively iodinated to provide the 5-
iodoimidazole XXVII. That imidazole may then be protected
and coupled to a suitably substituted benzyl moiety to provide
intermediate XXVIII. Attachment of the imidazolyl nitrogen
10   via an ethyl linker to the piperazine nitrogen of intermediate
XXI, described above, provides the instant compound XXIX.

Compounds of the instant invention wherein the
$A^1(CR^{1a}_2)_nA^2(CR^{1a}_2)_n$ linker is oxygen may be synthesized by
methods known in the art, for example as shown in Scheme 10.
15   The suitably substituted phenol XXX may be reacted with
methyl N-(cyano)methanimidate to provide the 4-phenoxy-
imidazole XXXI. After selective protection of one of the
imidazolyl nitrogens, the intermediate XXXII can undergo
alkylation reactions as described for the benzylimidazoles in
20   Scheme 9.

If the piperazine VIII is reductively alkylated with an
aldehyde which also has a protected hydroxyl group, such as
XXXIII in Scheme 11, the protecting groups can be subsequently
removed to unmask the hydroxyl group. The Boc protected amino
25   alcohol XXXIV can then be utilized to synthesize 2-aziridinyl-
methylpiperazines such as XXXV.

5-Substituted piperazin-2-ones can be prepared as
shown in Scheme 12. Reductive amination of Boc-protected
amino aldehydes XXXVI (prepared from I as illustrated) gives
30   rise to compound XXXVII. This is then reacted with bromoacetyl
bromide under Schotten-Baumann conditions; ring closure is
effected with a base such as sodium hydride in a polar aprotic
solvent such as dimethylformamide to give XXXVIII. The
carbamate protecting group is removed under acidic conditions

such as trifluoroacetic acid in methylene chloride, or hydrogen
chloride gas in methanol or ethyl acetate, and the resulting
piperazine can then be carried on to final products as described
in above.

5   The isomeric 3-substituted piperazin-2-ones can be
prepared as described in Scheme 13. The imine formed from
arylcarboxamides IXL and 2-aminoglycinal diethyl acetal (XL) can
be reduced under a variety of conditions, including sodium
triacetoxyborohydride in dichloroethane, to give the amine XLI.

10   A suitably substituted amino acid I can be coupled to amine XLI
under standard conditions, and the resulting amide XLII when
treated with aqueous acid in tetrahydrofuran can cyclize to the
unsaturated XLIII. Catalytic hydrogenation under standard
conditions gives the requisite intermediate XLIV, which is

15   elaborated to final products as described in above.

Reaction Scheme 14 provides an illustrative example
of the synthesis of compounds of the instant invention wherein
the substituents R^2 and R^3 are combined to form - $(CH_2)_u$ -. For
example, 1-aminocyclohexane-1-carboxylic acid XLV can be

20   converted to the spiropiperazine XLVI essentially according to
the procedures outlined in Schemes 1 and 2. The piperazine
intermediate XLVI can be deprotected as before, and carried on to
final products as described in Schemes 3-8. It is understood that
reagents utilized to provide the imidazolylalkyl substituent may

25   be readily replaced by other reagents well known in the art and
readily available to provide other N-substituents on the
piperazine.

Scheme 15 illustrates the use of an optionally
substituted homoserine lactone XLVII to prepare a Boc-protected

30   piperazinone XLVIII. Intermediate XLVIII may be deprotected
and reductively alkylated or acylated as illustrated in the
previous Schemes. Alternatively, the hydroxyl moiety of
intermediate XLVIII may be mesylated and displaced by a suitable
nucleophile, such as the sodium salt of ethane thiol, to provide an

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intermediate IL. Intermediate XLVIII may also be oxidized to provide the carboxylic acid on intermediate L, which can be utilized form an ester or amide moiety.

5   Amino acids of the general formula LI which have a sidechain not found in natural amino acids may be prepared by the reactions illustrated in Scheme 16 starting with the readily prepared imine LII.

Schemes 17-20 illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant
10   compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art. For example, Scheme 21 illustrates the preparation of the corresponding quinoline aldehyde.

15   Scheme 22 depicts a general method for synthesizing a key intermediate useful in the preparation of a preferred embodiments of the instant invention wherein V is phenyl and W is imidazole. A piperazine moiety can be readily added to this benzyl-imidazole intermediate as set forth in Scheme 23.

20

SCHEME 1

SCHEME 2

$$Z'(CH_2)_v - \overset{O}{\underset{\|}{C}} - OH$$

Structure VI

$$\xrightarrow[\substack{\text{EDC} \\ \text{HOBT, DIEA}}]{}$$

Structure VII

$$\xrightarrow[]{\text{HCl, EtOAc}}$$

Structure VIII
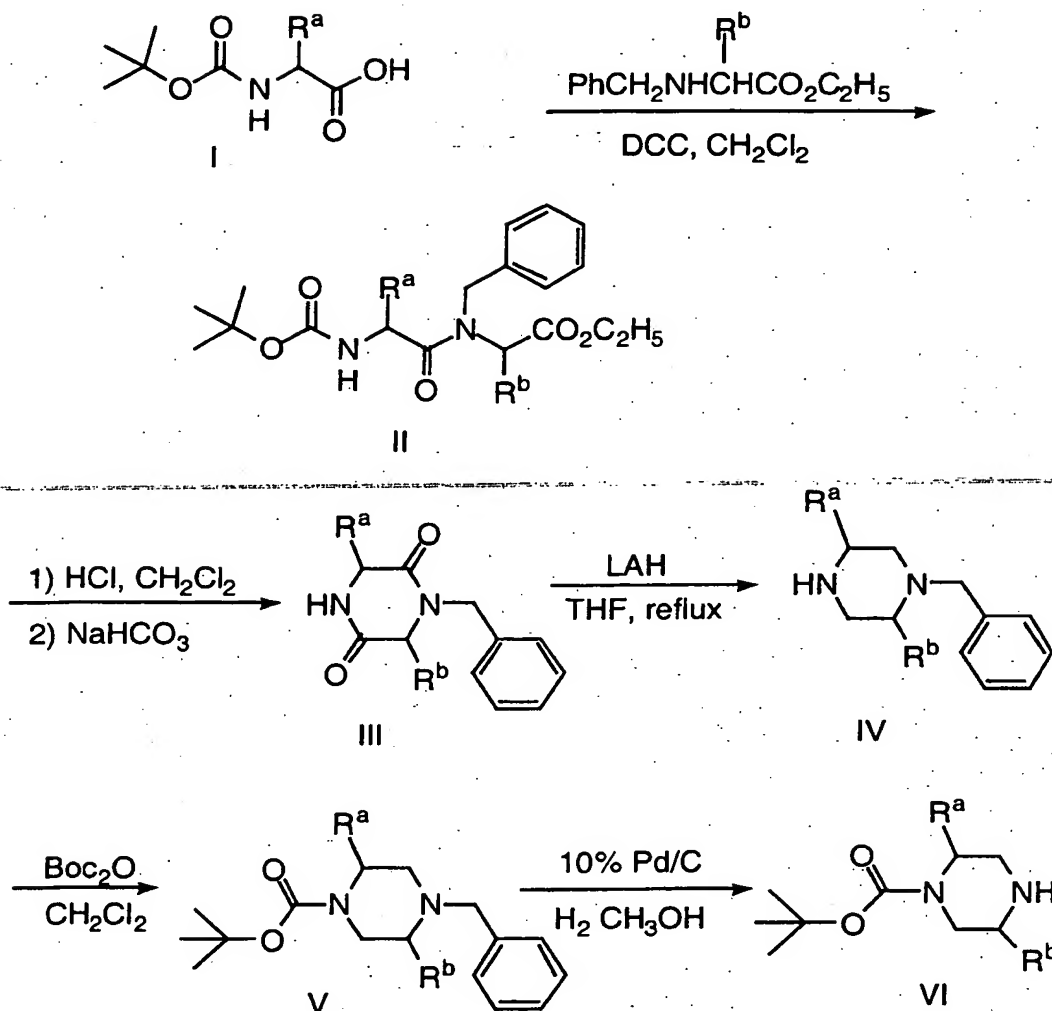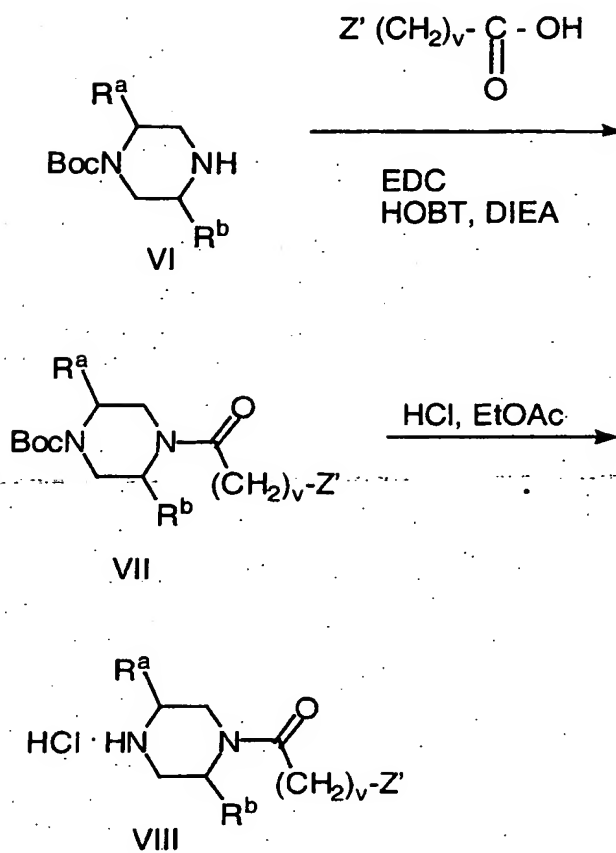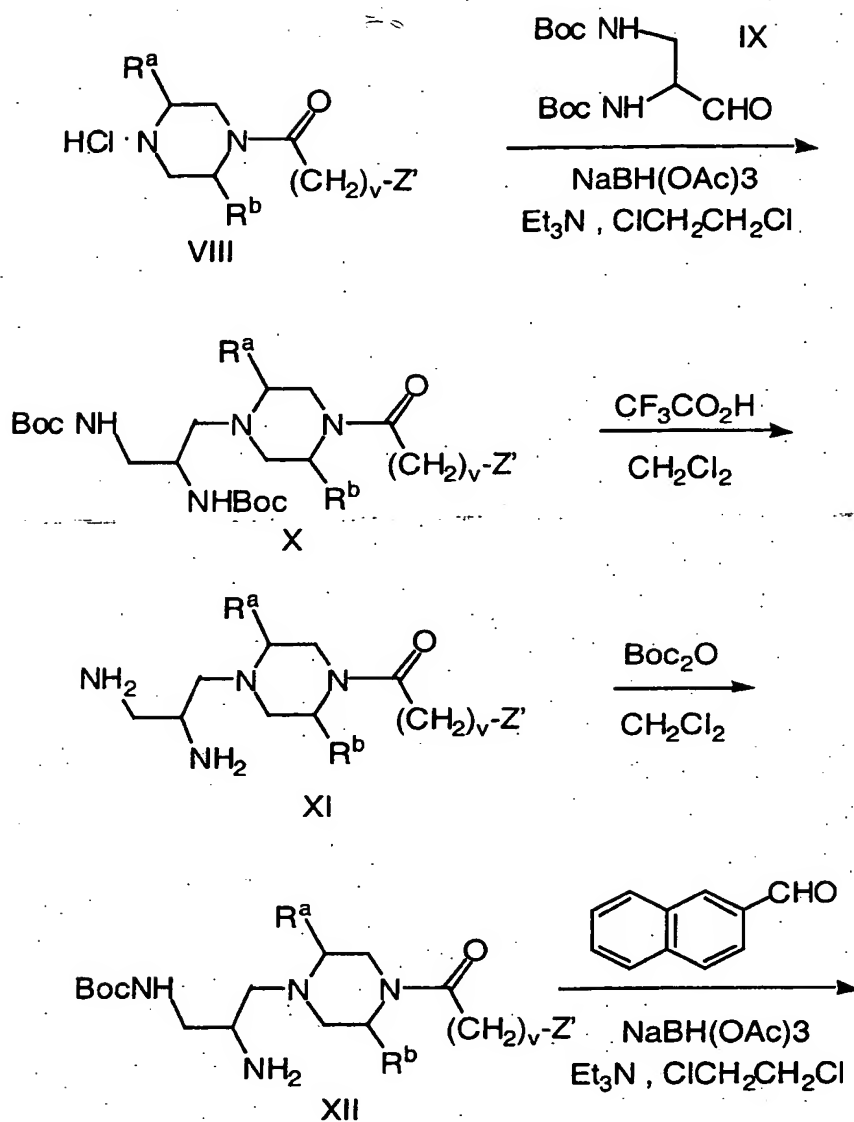
SCHEME 3

SCHEME 3 (continued)

SCHEME 4

$NaBH(OAc)_3$
Et_3N , $ClCH_2CH_2Cl$

R^a

$HCl \cdot$ N   N

$(CH_2)_v$-Z'

R^b

VIII

$(CH_2)_n CHO$

Tr

R^a

$(CH_2)_{n+1}$

$(CH_2)_v$-Z'

R^b

Tr

XVI

1) Ar CH_2X, CH_3CN
2) CF_3CO_2H, CH_2Cl_2
   $(C_2H_5)_3SiH$

CF_3CO_2H, CH_2Cl_2
$(C_2H_5)_3SiH$

R^a

$(CH_2)_{n+1}$

$(CH_2)_v$-Z'

R^b

N
H

XVII

R^a

Ar

$(CH_2)_{n+1}$

$(CH_2)_v$-Z'

R^b

N

XVIII

-60-

SCHEME 5

-61-

<u>SCHEME 6</u>

XXIII

XXIV

XXV

SCHEME 7

SCHEME 8

intermediate A

SCHEME 8 (continued)

1. aq. LiOH

BH$_3$

DMSO, (F$_3$CCO)$_2$O

−78°

intermediate A

NaBH(OAc)$_3$

Et$_3$N , ClCH$_2$CH$_2$Cl

-65-
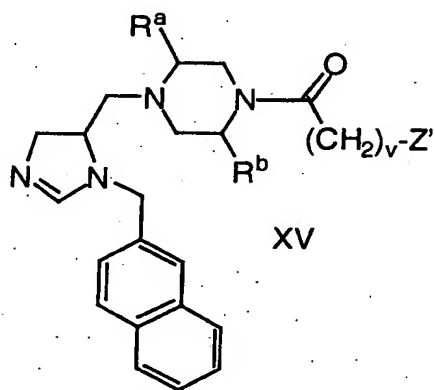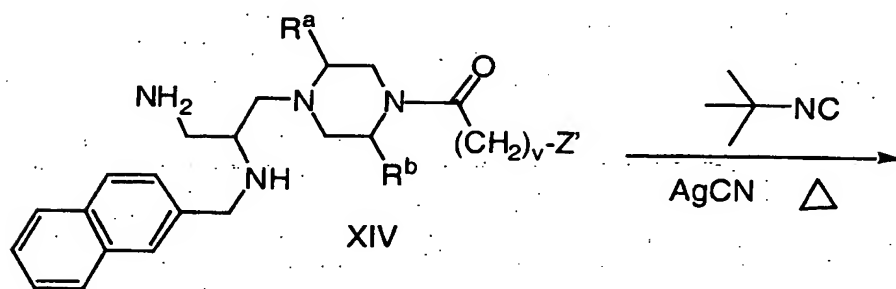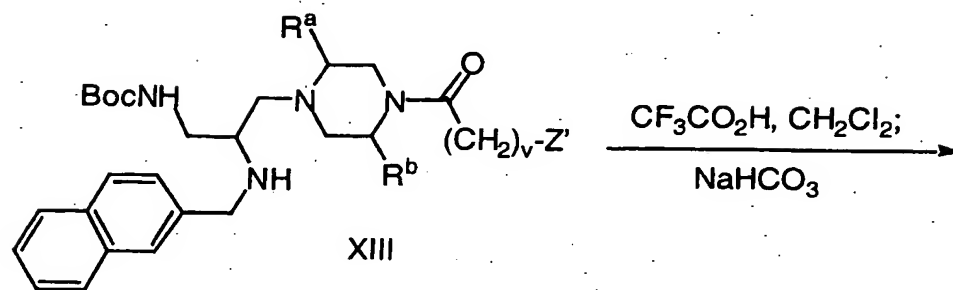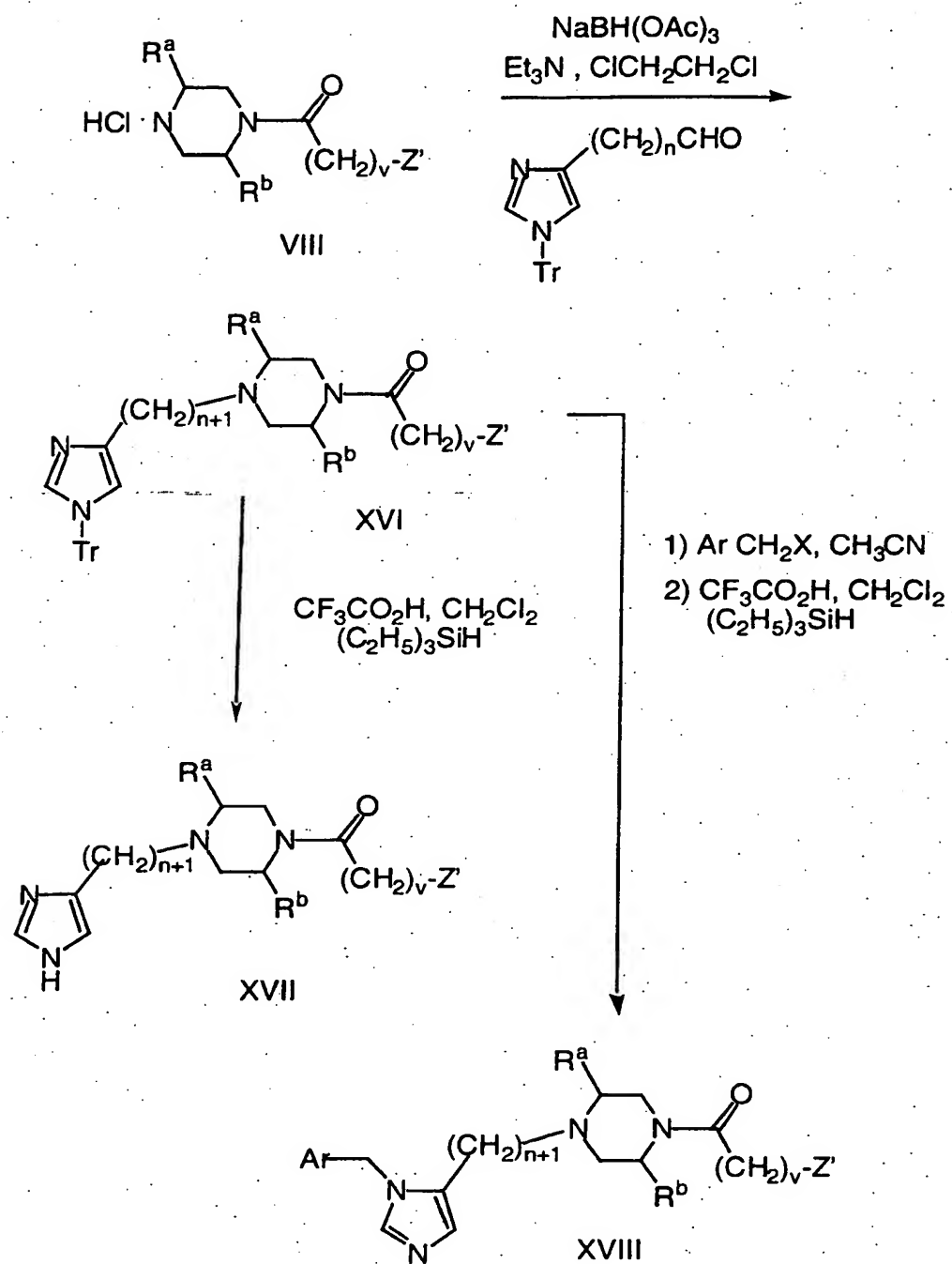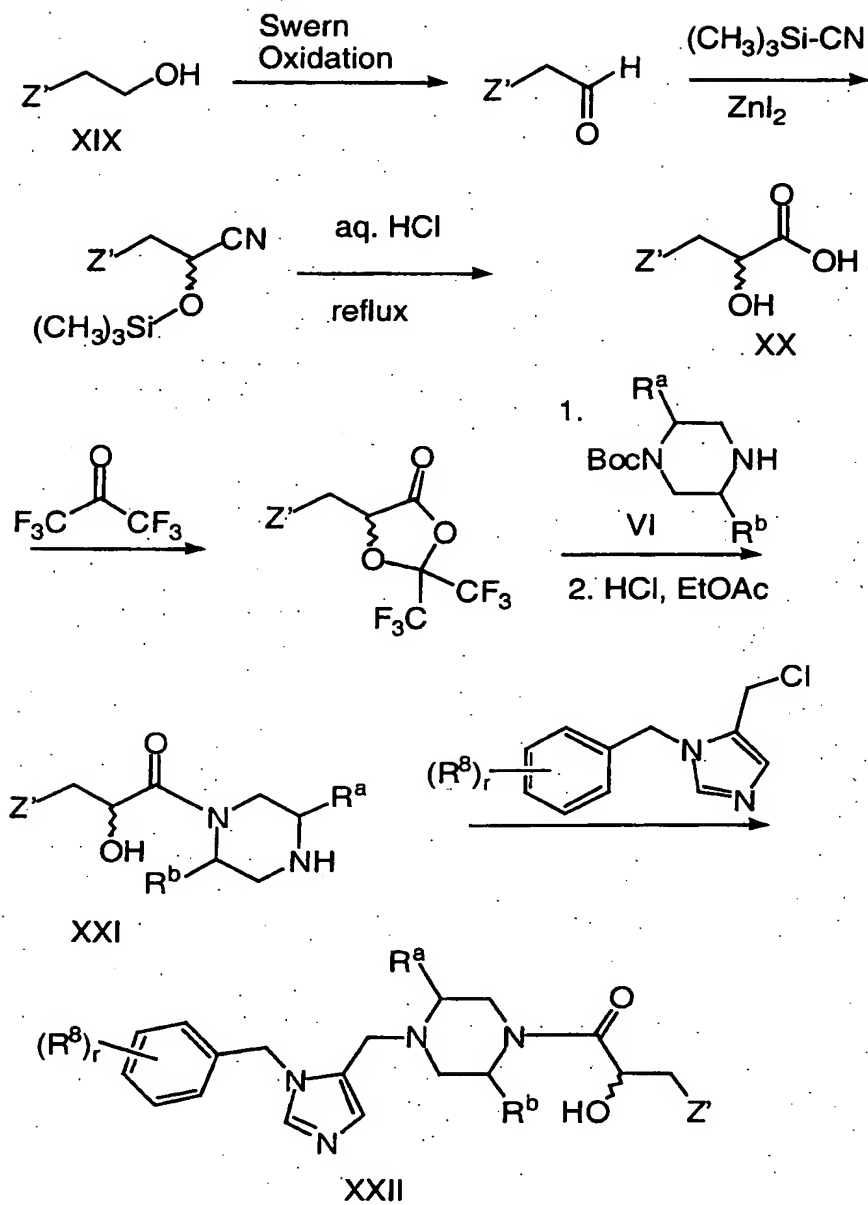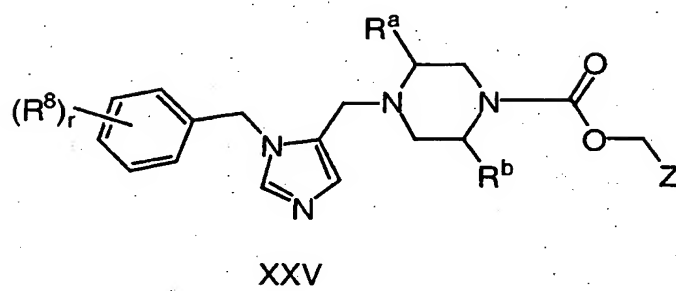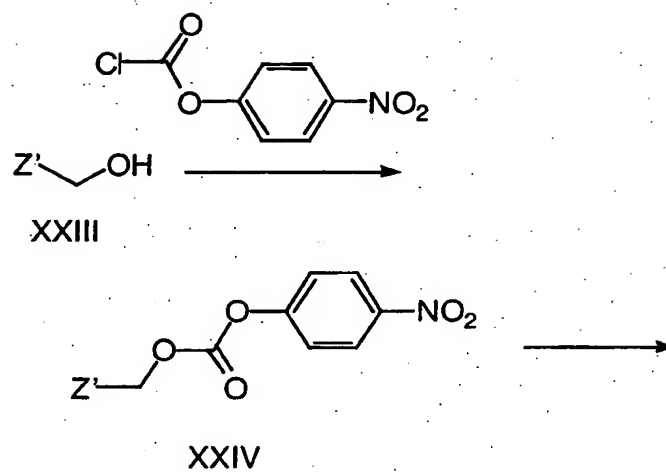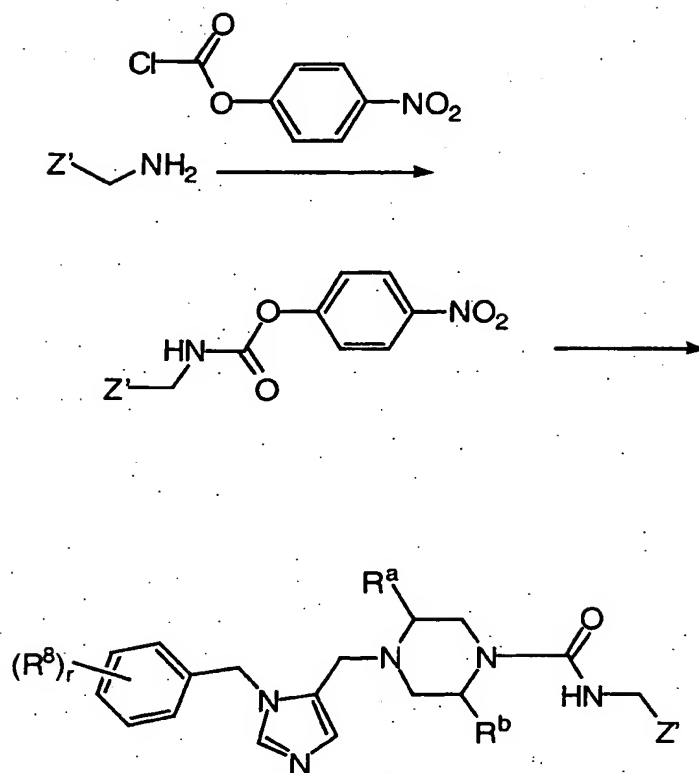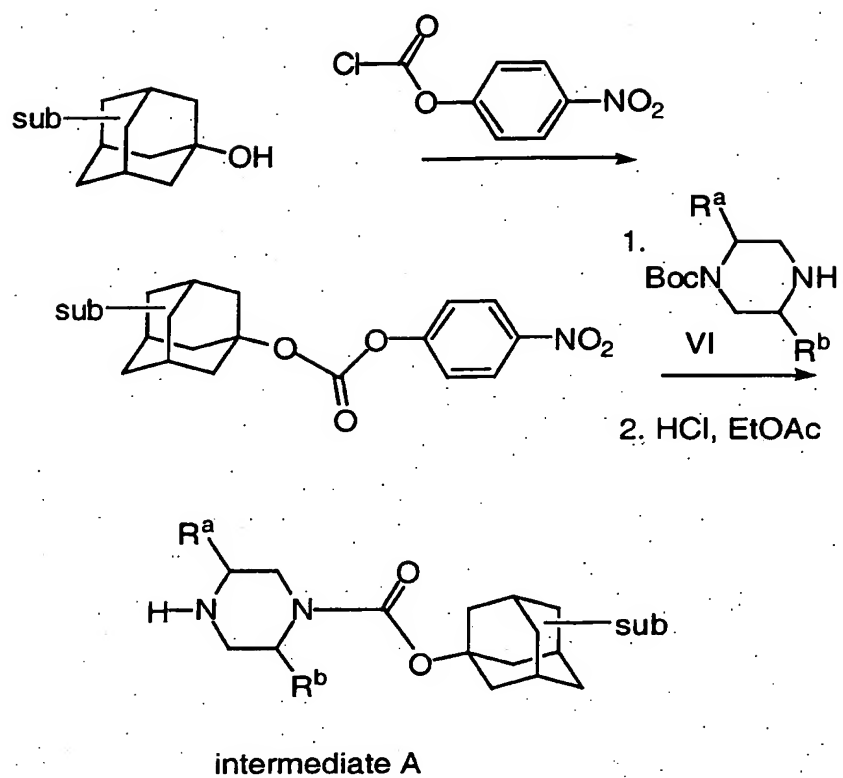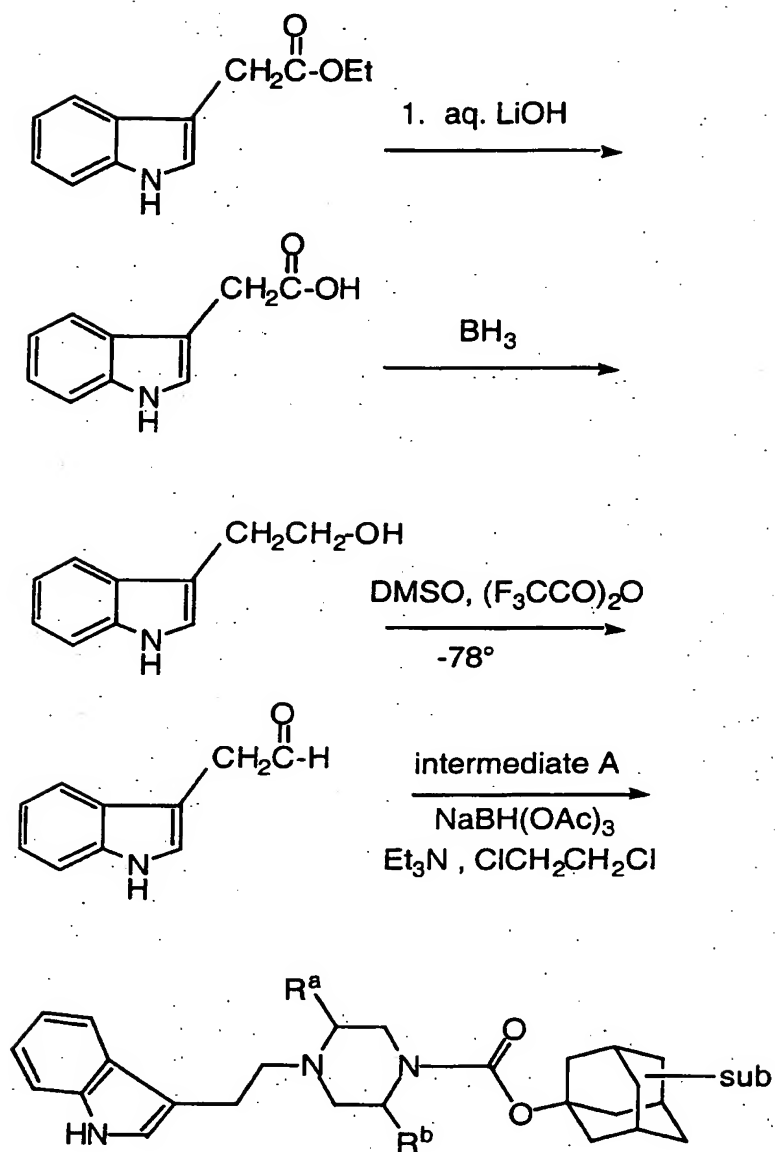
SCHEME 9

SCHEME 9 (continued)

BH$_3$

Swern
oxidation

XXI

NaBH(OAc)$_3$
Et$_3$N , ClCH$_2$CH$_2$Cl

XXIX

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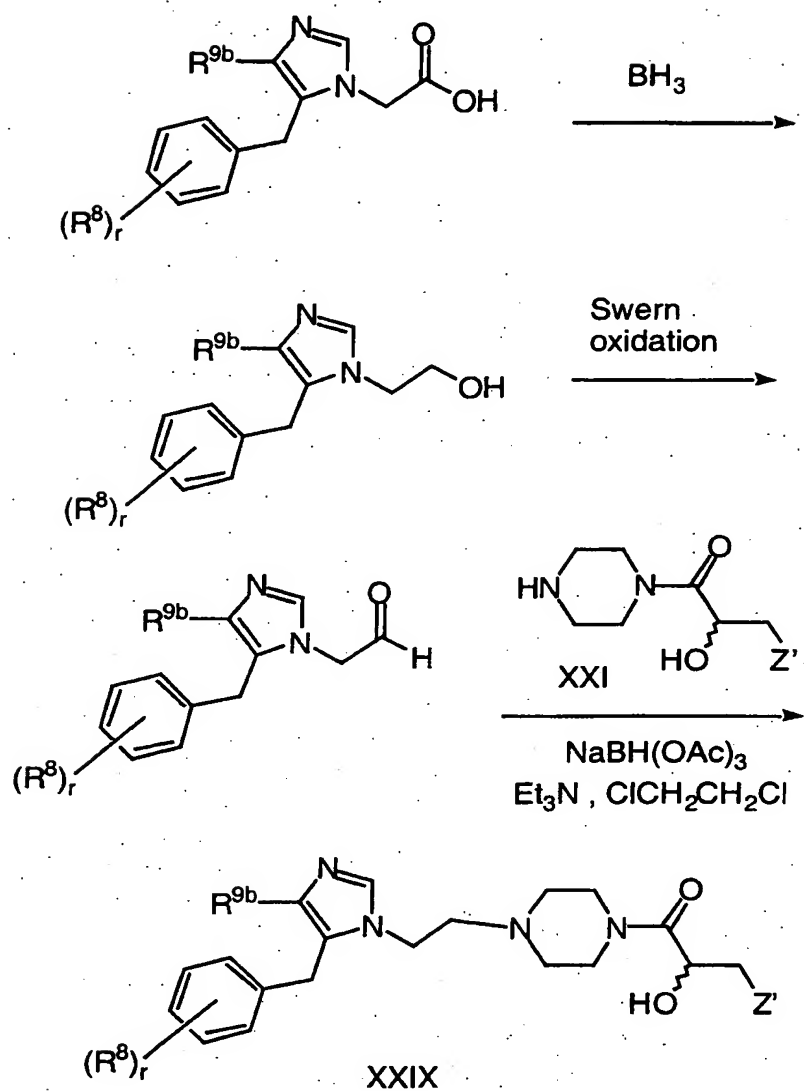
SCHEME 10

SCHEME 11

SCHEME 12

$$\text{(I)} \xrightarrow[\substack{\text{EDC . HCl, HOBT} \\ \text{DMF, Et}_3\text{N, pH 7}}]{\text{CH}_3\text{NHOCH}_3 \cdot \text{HCl}}$$

$$\xrightarrow{\text{LAH, Et}_2\text{O}}$$

XXXVI

$$\xrightarrow[\substack{\text{NaBH(OAc)}_3 \\ \text{ClCH}_2\text{CH}_2\text{Cl} \\ \text{pH 6}}]{\text{H}_2\text{N-(CR}^{1c}_2)_v\text{-Z'}}$$

XXXVII

$$\xrightarrow[\substack{\text{2) NaH, THF, DMF}}]{\substack{\text{1) BrCH}_2\text{COBr} \\ \text{EtOAc, H}_2\text{O, NaHCO}_3}}$$

-70-
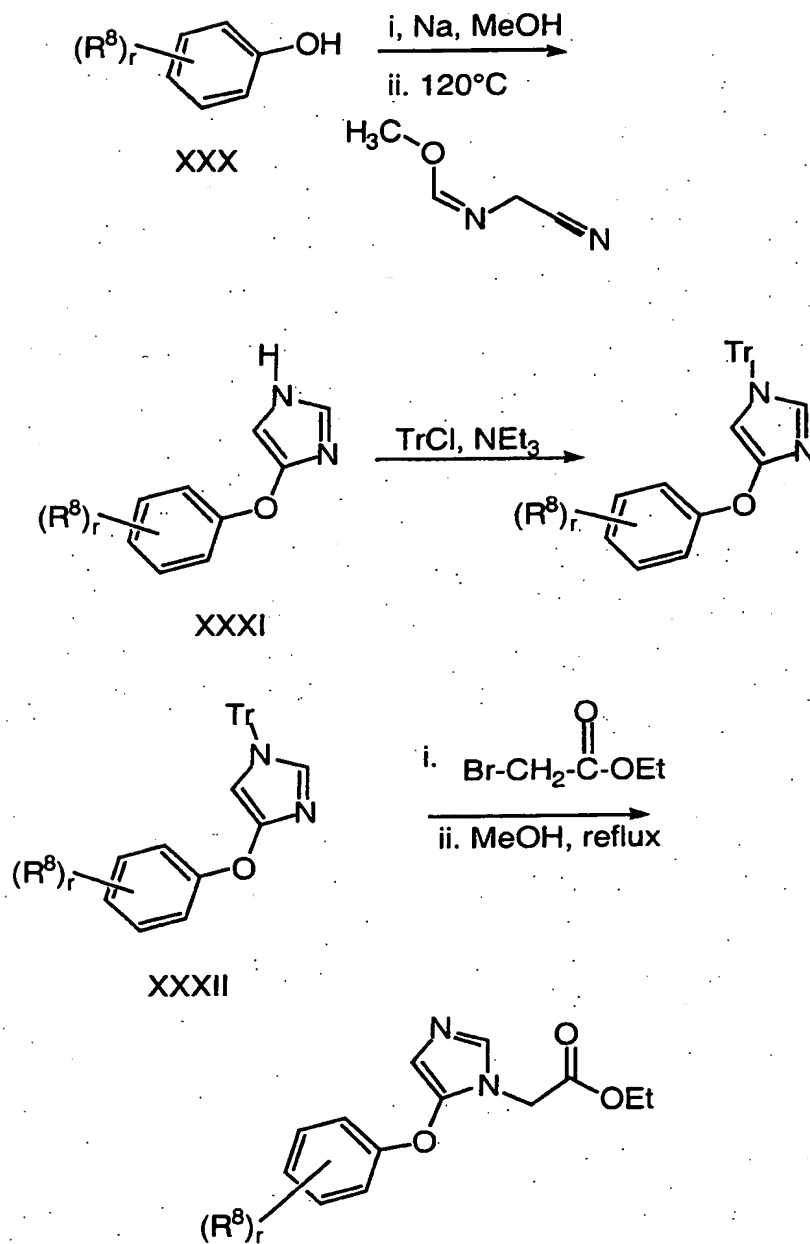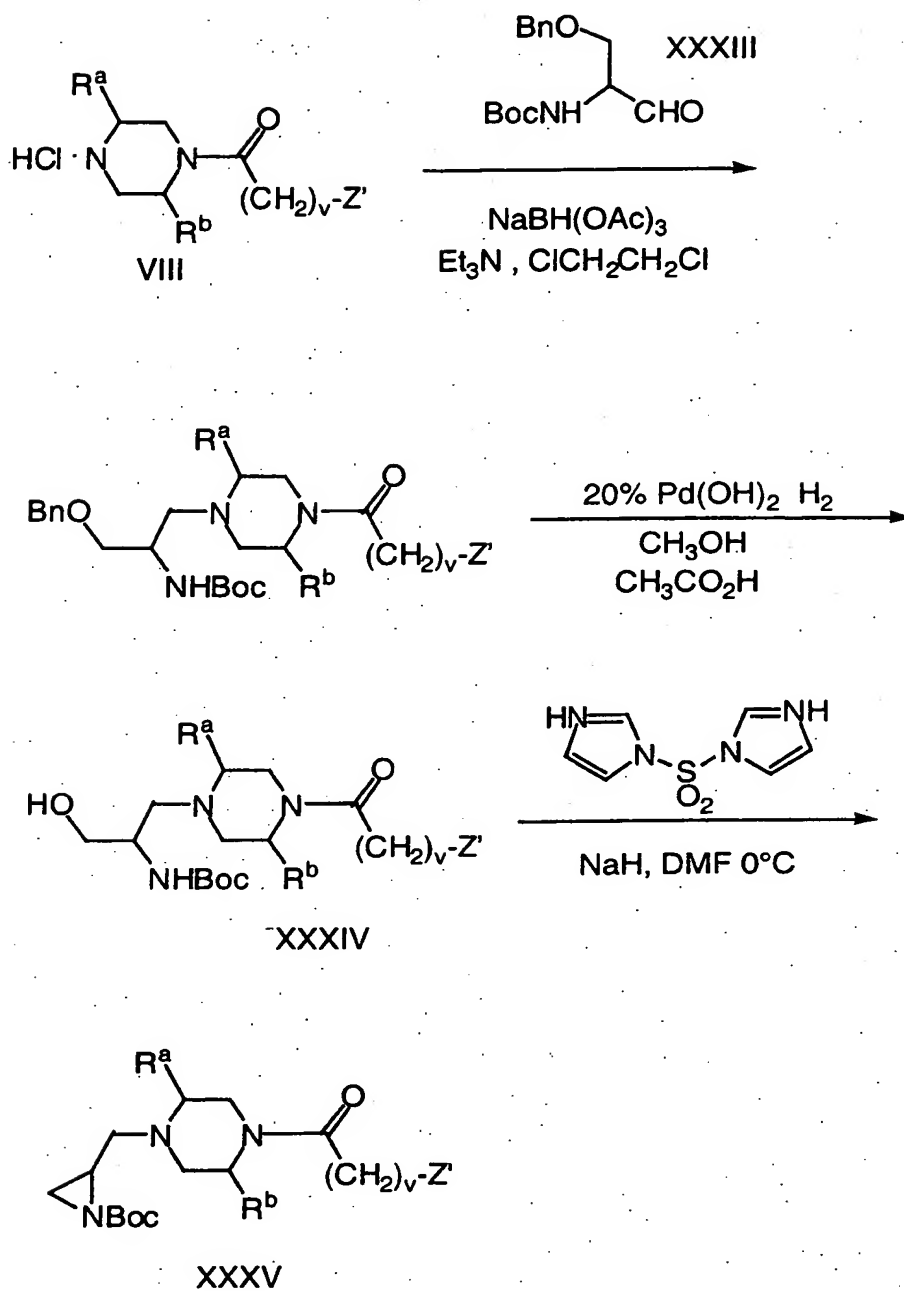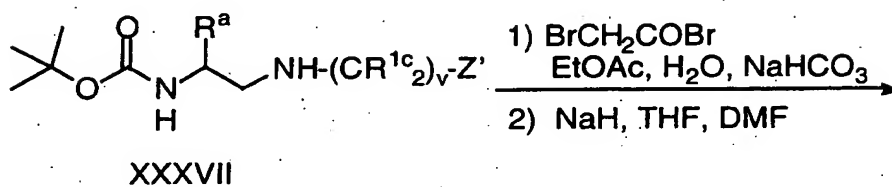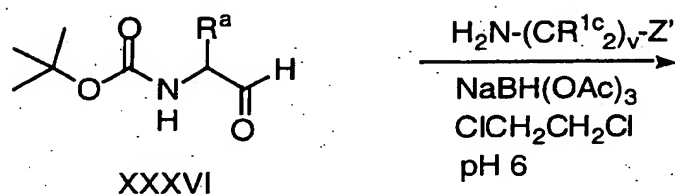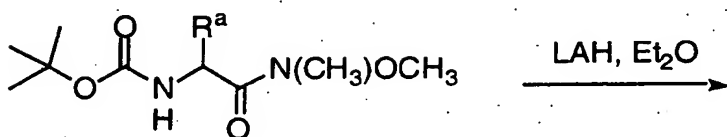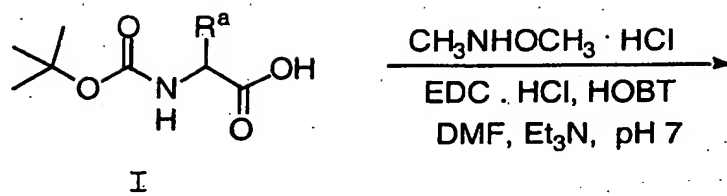
SCHEME 12 (continued)

XXXVIII

1) TFA, CH_2Cl_2

SCHEME 13

Z'-CHO + $NH_2CH_2CH(OC_2H_5)_2$ $\xrightarrow{NaBH(OAc)_3}$

IXL   XL

Z'-CH$_2$NHCH$_2$CH(OC$_2$H$_5$)$_2$

XLI

$$\xrightarrow[\text{DMF, Et}_3\text{N, pH 7}]{\text{EDC . HCl, HOBT}}$$

(Compound I: tert-butyl carbamate with R^a and COOH)

XLII

$$\xrightarrow[\text{THF}]{\text{6N HCl}}$$

XLIII

$$\xrightarrow[\text{CH}_3\text{OH}]{\text{H}_2 \ 10\%\text{Pd/C}}$$

XLIV
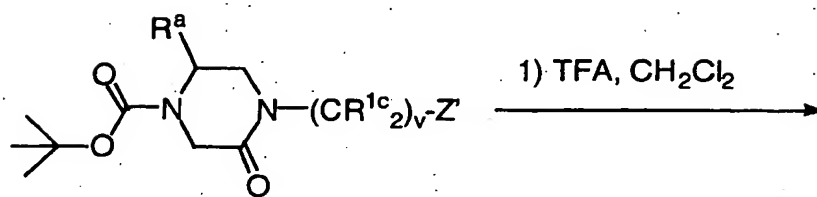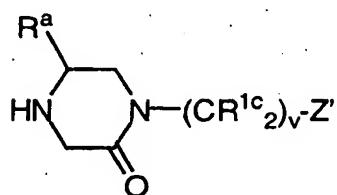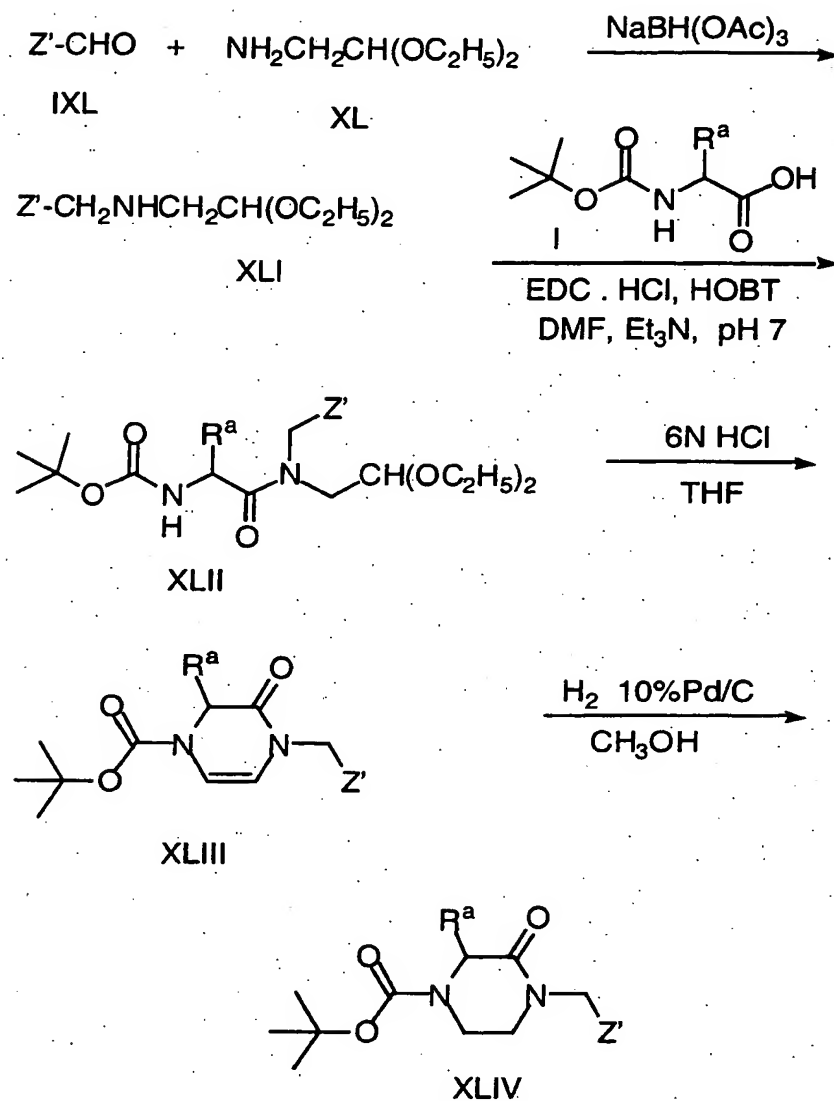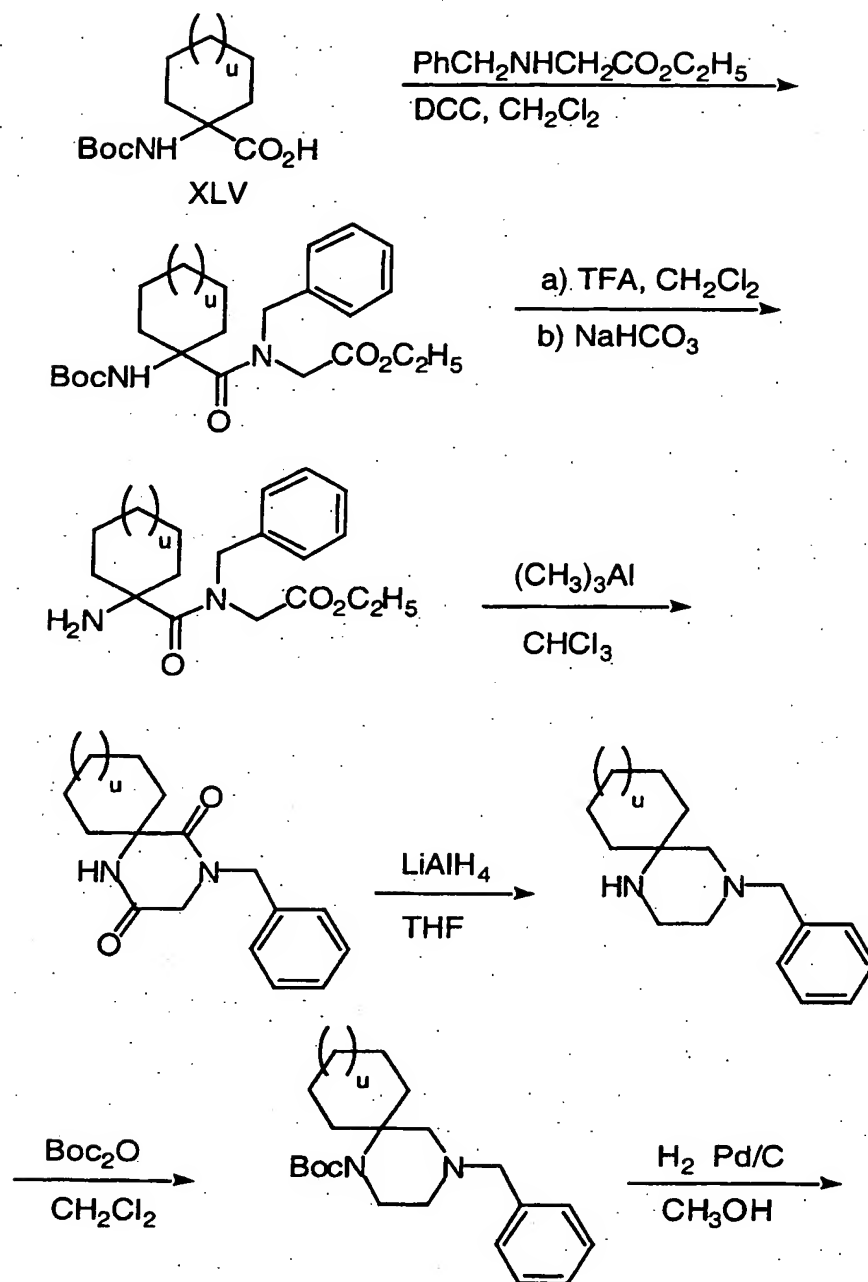
SCHEME 14

SCHEME 14 (continued)
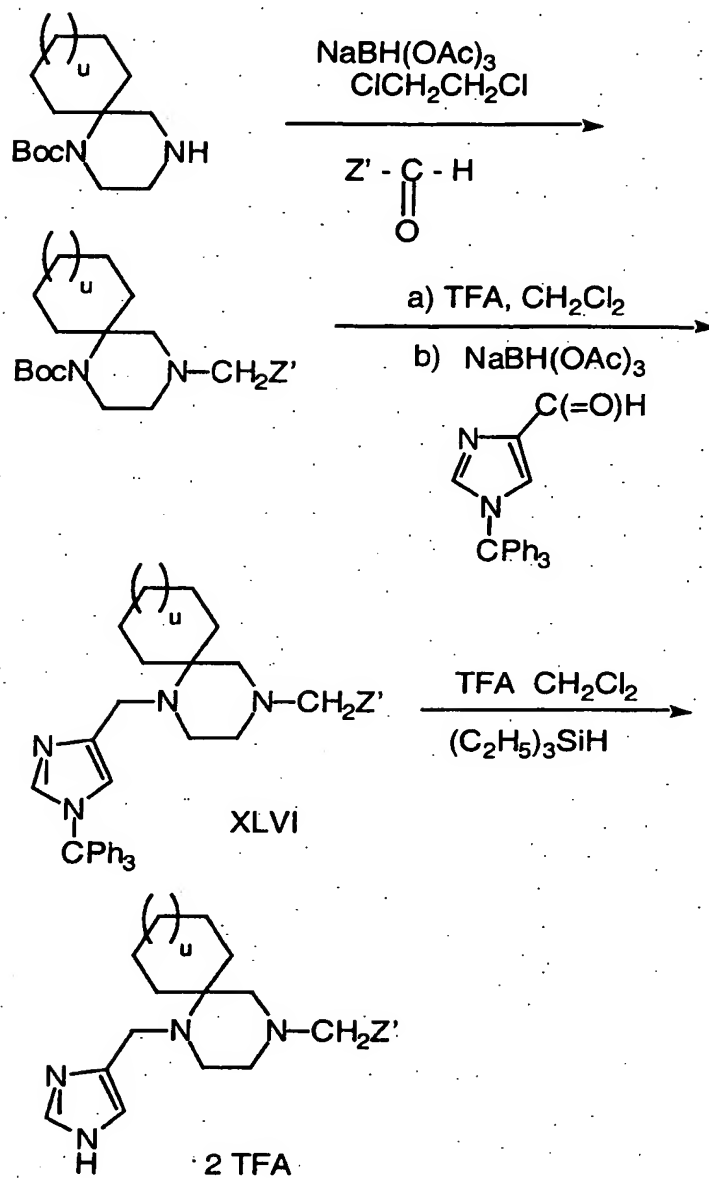
SCHEME 15

SCHEME 15 (continued)

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SCHEME 16

1. KOtBu, THF
R^{2}X

2. 5% aqueous HCl

LII

1. Boc$_2$O, NaHCO$_3$

2. LiAlH$_4$, Et$_2$O

LI

SCHEME 17

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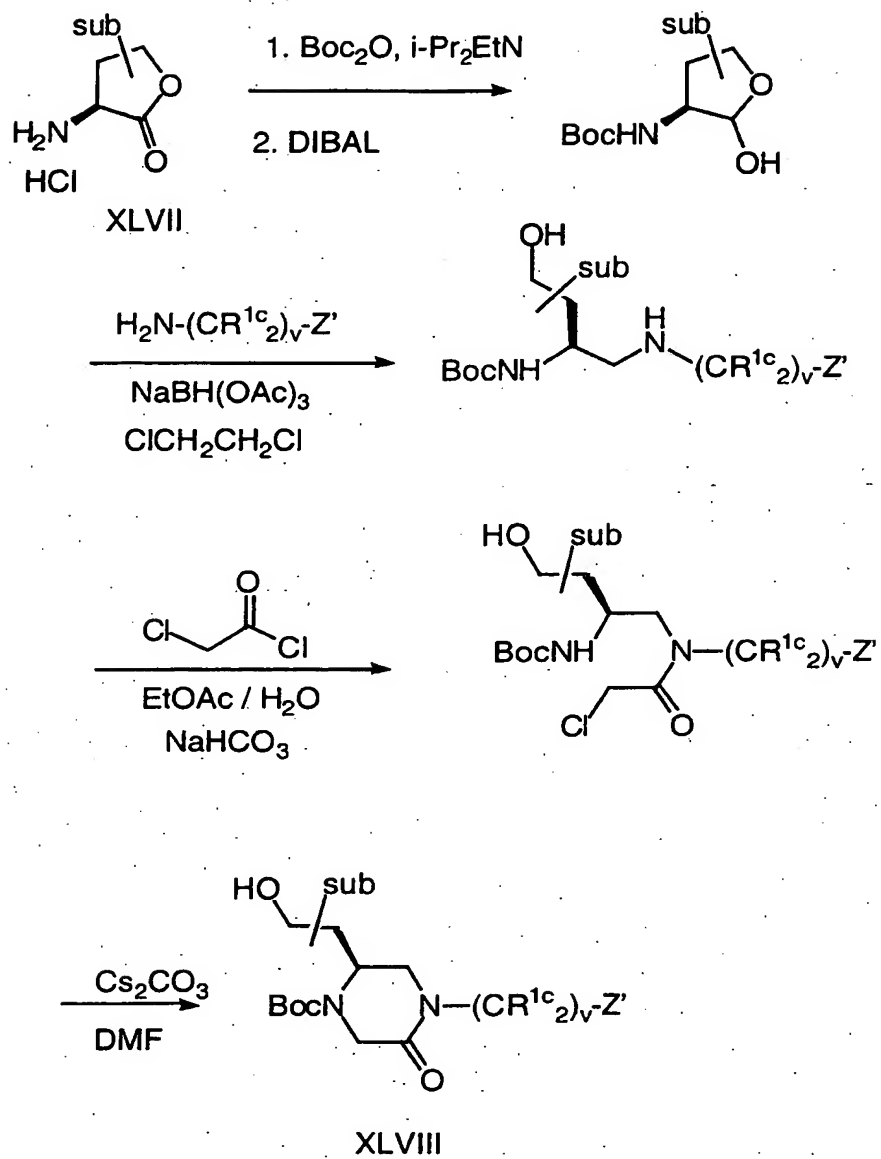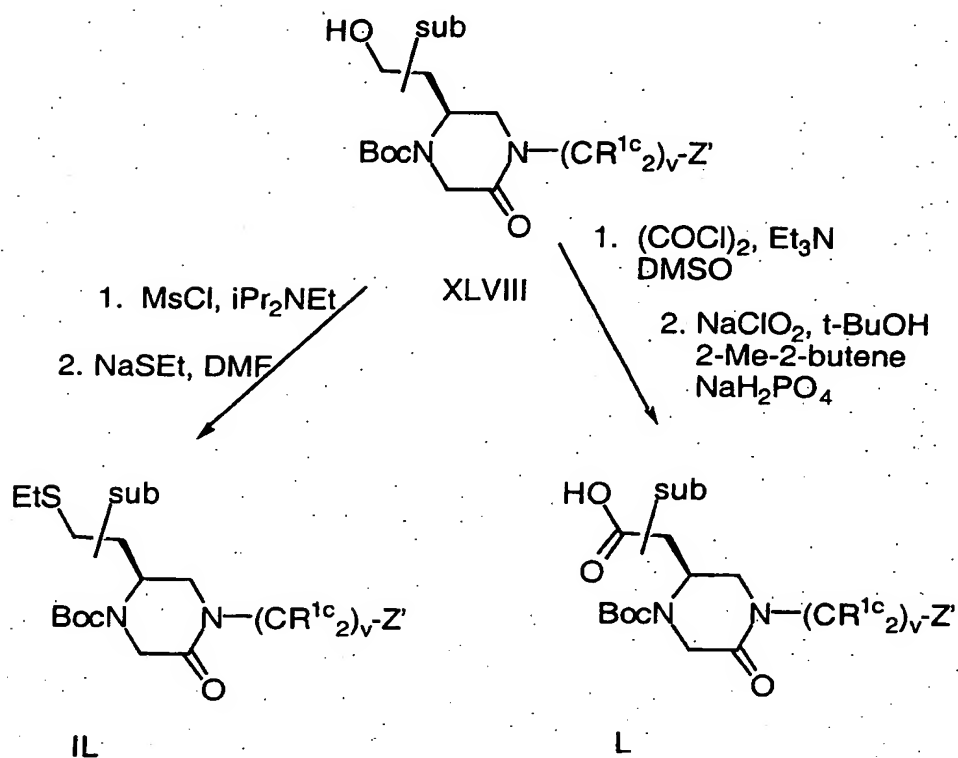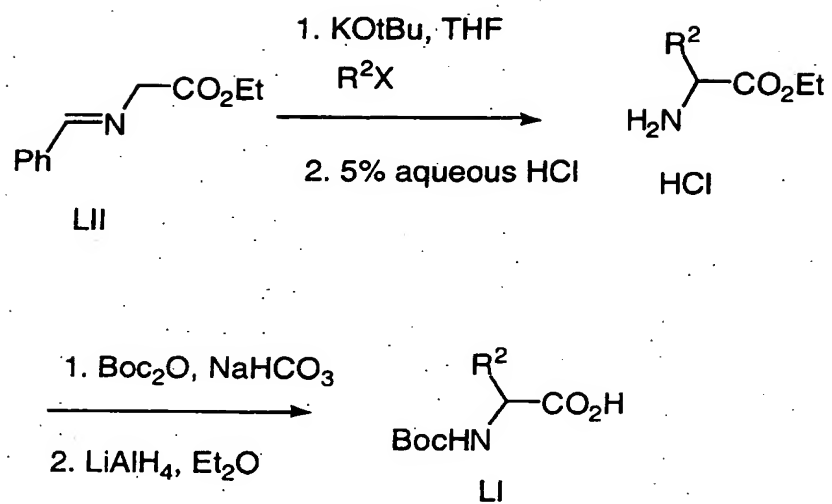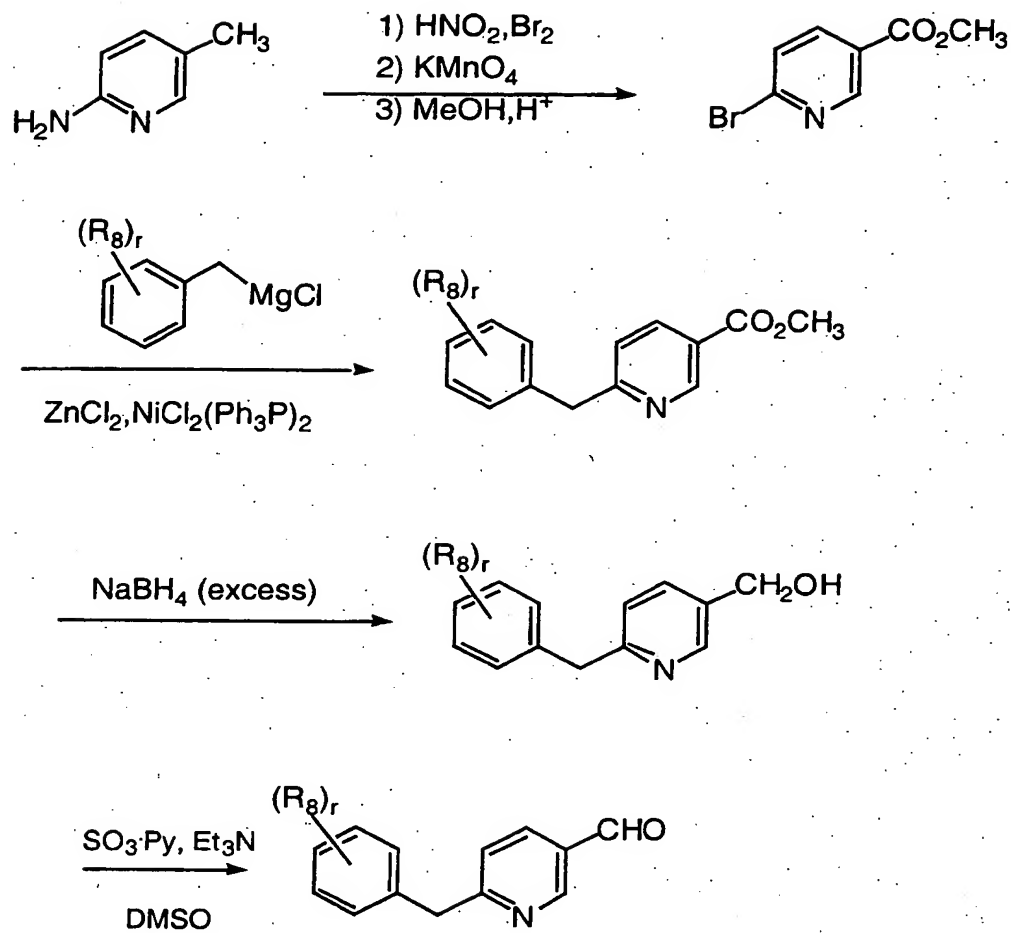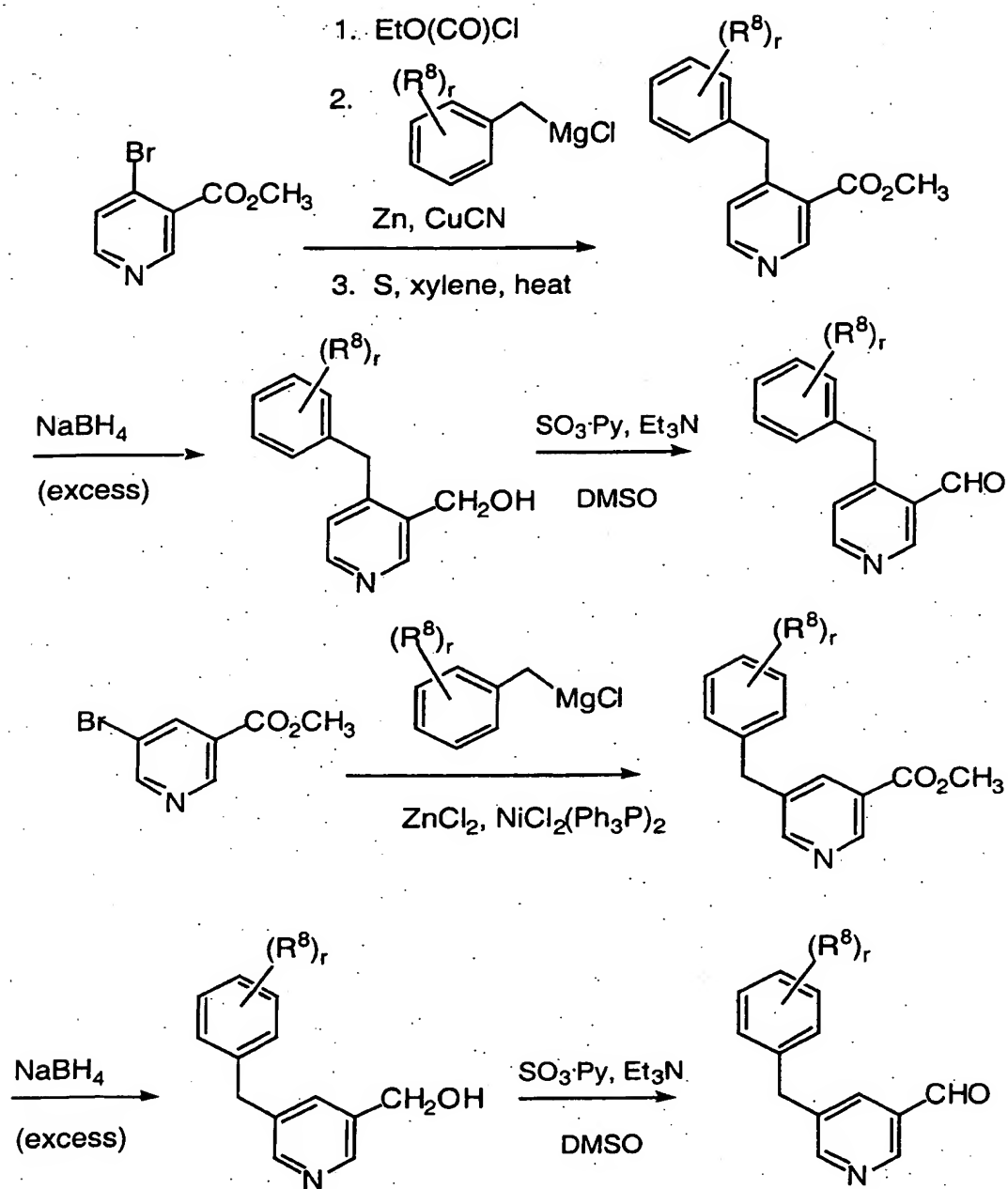
SCHEME 18

SCHEME 19

SCHEME 20

SCHEME 21

5

SCHEME 22

SCHEME 23

diisopropylethyl amine

H$_2$, 10% Pd/C

EtOH
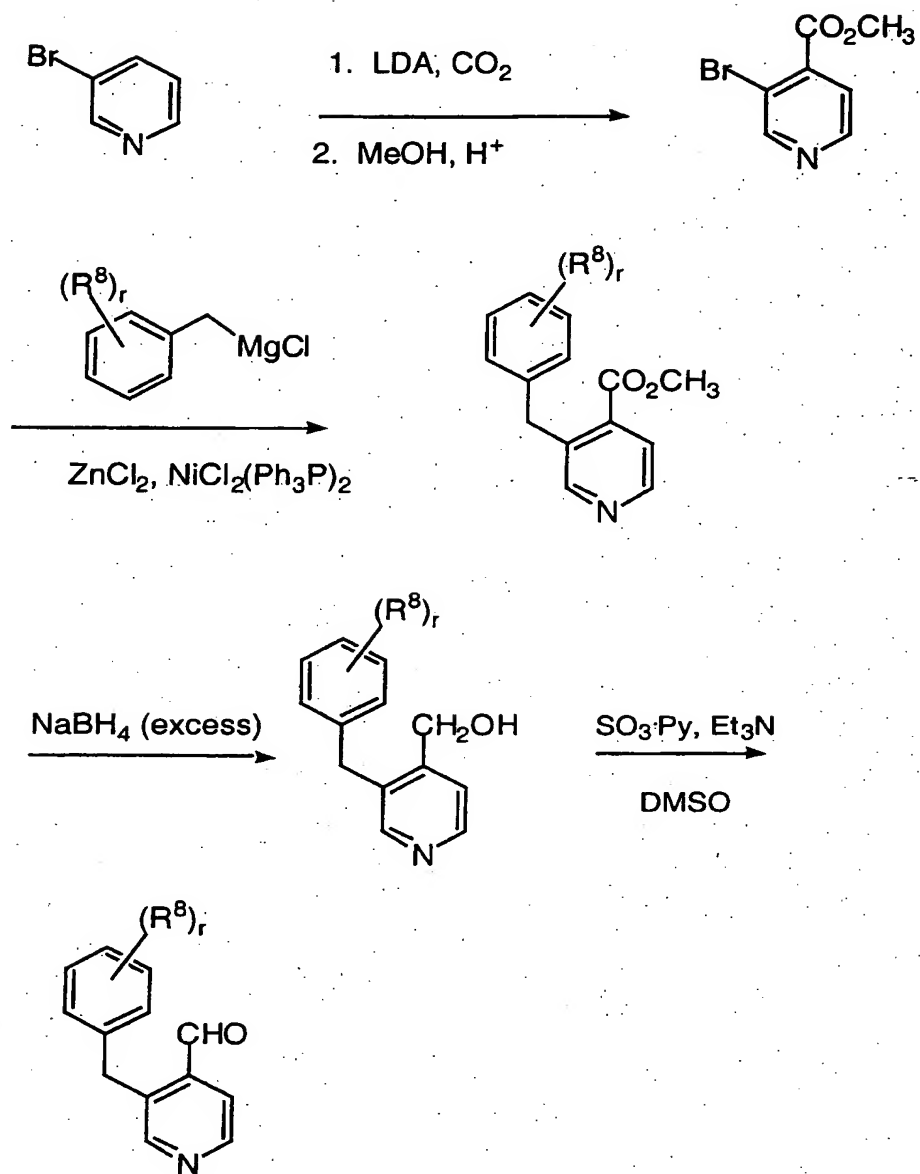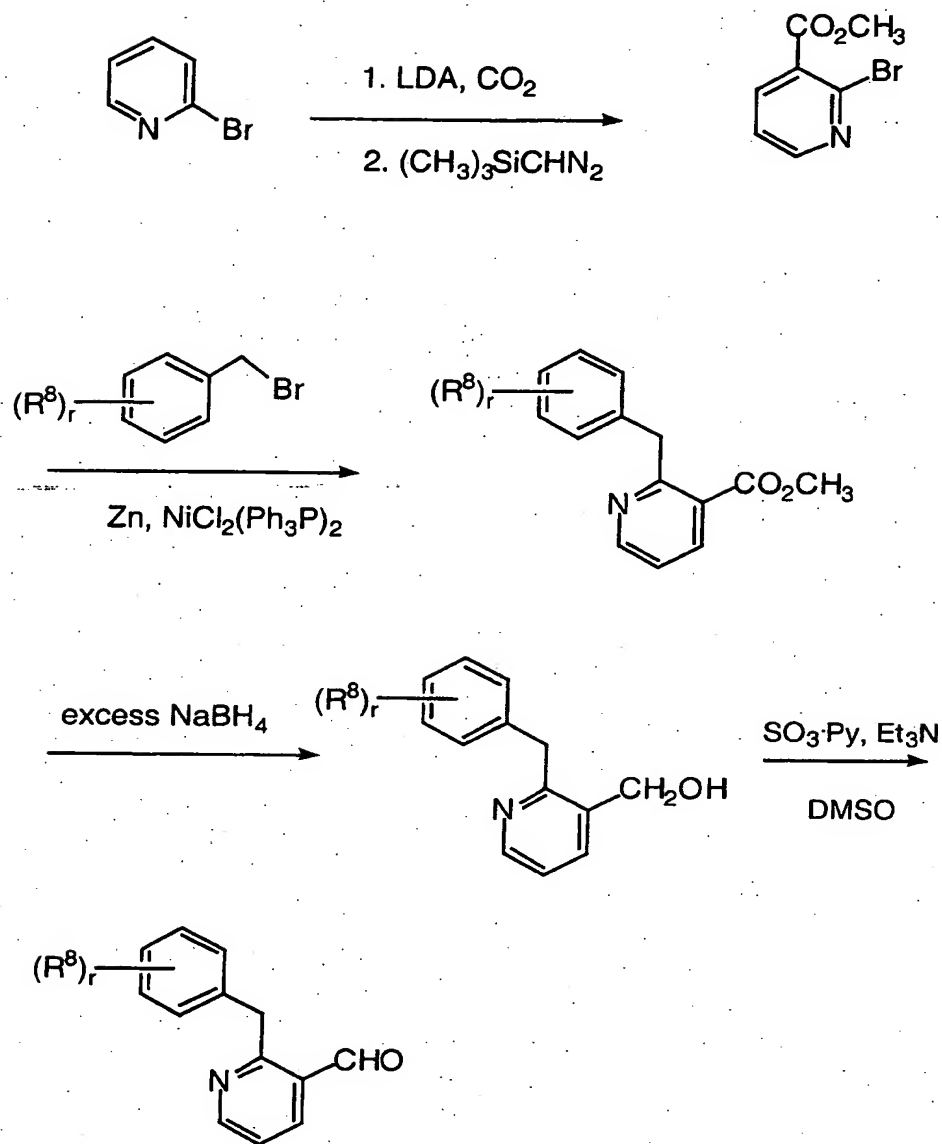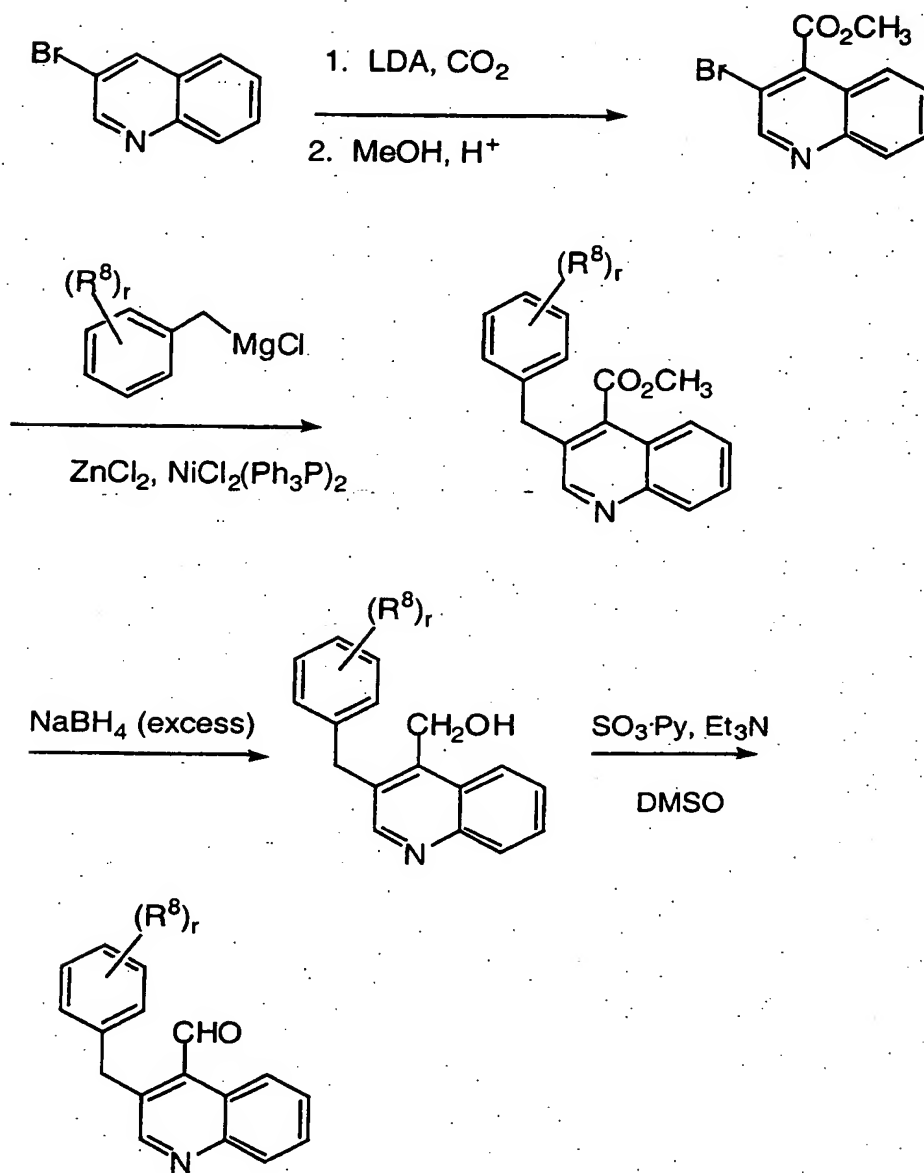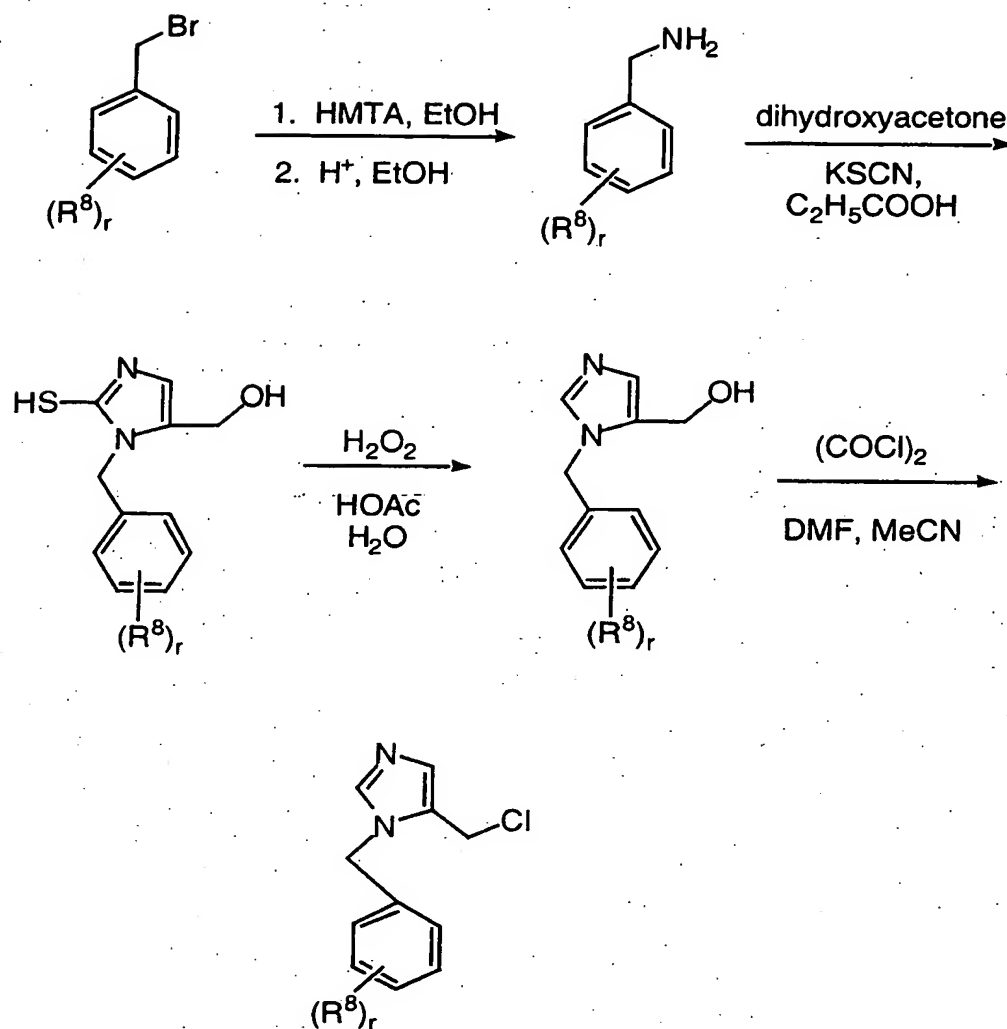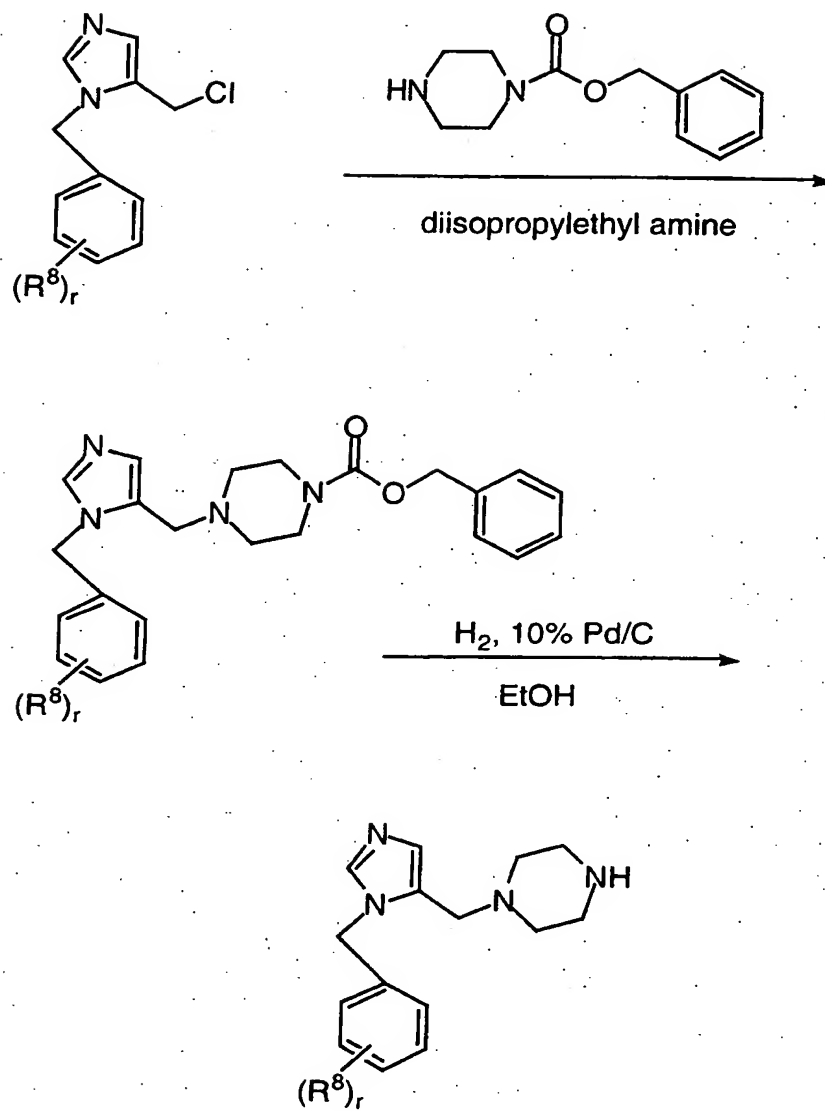
The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with

5   the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the ras genes themselves, mutations in the proteins that can regulate Ras activity (i.e., neurofibromin (NF-1), neu, src,

10   abl, lck, fyn) or by other mechanisms.

The compounds of the instant invention inhibit prenyl-protein transferase and the prenylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al.

15   Cancer Research, 55: 4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of vision deficit related to retinal vascularization.

The compounds of this invention are also useful for

20   inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an

25   effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the

30   treatment of hepatitis delta and related viruses (J.S. Glenn et al. Science, 256:1331-1333 (1992).

The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous

transluminal coronary angioplasty by inhibiting neointimal
formation (C. Indolfi et al. Nature medicine, 1:541-545(1995).

     The instant compounds may also be useful in the
treatment and prevention of polycystic kidney disease (D.L.

5   Schaffner et al. American Journal of Pathology, 142:1051-1060
(1993) and B. Cowley, Jr. et al.FASEB Journal, 2:A3160 (1988)).

     The instant compounds may also be useful for the
treatment of fungal infections.

     The instant compounds may also be useful as

10 inhibitors of proliferation of vascular smooth muscle cells and
therefore useful in the prevention and therapy of arteriosclerosis
and diabetic vascular pathologies.

     The compounds of this invention may be administered
to mammals, preferably humans, either alone or, preferably, in

15 combination with pharmaceutically acceptable carriers,
excipients or diluents, in a pharmaceutical composition,
according to standard pharmaceutical practice. The compounds
can be administered orally or parenterally, including the
intravenous, intramuscular, intraperitoneal, subcutaneous, rectal

20 and topical routes of administration.

     The pharmaceutical compositions containing the
active ingredient may be in a form suitable for oral use, for
example, as tablets, troches, lozenges, aqueous or oily
suspensions, dispersible powders or granules, emulsions, hard or

25 soft capsules, or syrups or elixirs. Compositions intended for oral
use may be prepared according to any method known to the art
for the manufacture of pharmaceutical compositions and such
compositions may contain one or more agents selected from the
group consisting of sweetening agents, flavoring agents, coloring

30 agents and preserving agents in order to provide pharma-
ceutically elegant and palatable preparations. Tablets contain
the active ingredient in admixture with non-toxic pharma-
ceutically acceptable excipients which are suitable for the
manufacture of tablets. These excipients may be for example,

inert diluents, such as calcium carbonate, sodium carbonate,
lactose, calcium phosphate or sodium phosphate; granulating and
disintegrating agents, for example, microcrystalline cellulose,
sodium crosscarmellose, corn starch, or alginic acid; binding

5   agents, for example starch, gelatin, polyvinyl-pyrrolidone or
acacia, and lubricating agents, for example, magnesium stearate,
stearic acid or talc. The tablets may be uncoated or they may be
coated by known techniques to mask the unpleasant taste of the
drug or delay disintegration and absorption in the gastro-

10 intestinal tract and thereby provide a sustained action over a
longer period. For example, a water soluble taste masking
material such as hydroxypropylmethyl-cellulose or hydroxy-
propylcellulose, or a time delay material such as ethyl cellulose,
cellulose acetate buryrate may be employed.

15   Formulations for oral use may also be presented as
hard gelatin capsules wherein the active ingredient is mixed with
an inert solid diluent, for example, calcium carbonate, calcium
phosphate or kaolin, or as soft gelatin capsules wherein the active
ingredient is mixed with water soluble carrier such as polyethyl-

20 eneglycol or an oil medium, for example peanut oil, liquid
paraffin, or olive oil.
            Aqueous suspensions contain the active material in
admixture with excipients suitable for the manufacture of
aqueous suspensions. Such excipients are suspending agents, for

25 example sodium carboxymethylcellulose, methylcellulose,
hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-
pyrrolidone, gum tragacanth and gum acacia; dispersing or
wetting agents may be a naturally-occurring phosphatide, for
example lecithin, or condensation products of an alkylene oxide

30 with fatty acids, for example polyoxyethylene stearate, or
condensation products of ethylene oxide with long chain aliphatic
alcohols, for example heptadecaethylene-oxycetanol, or
condensation products of ethylene oxide with partial esters
derived from fatty acids and a hexitol such as polyoxyethylene

sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives,

5   for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

          Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil,

10   olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These

15   compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

          Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or

20   wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the

25   addition of an anti-oxidant such as ascorbic acid.

          The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these.

30   Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxy-

ethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose.
5   Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's
10   solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin.
15   The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution
20   or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous
25   pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using
30   those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition,

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sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of

5   injectables.

Compounds of Formula A may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary

10   temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

15   For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula A are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be

20   administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration

25   will, of course, be continuous rather than intermittent throughout the dosage regimen.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or

30   indirectly, from combination of the specific ingredients in the specified amounts.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage

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generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

5   In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

10   The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the compounds of the instant invention may also be co-administered with other 15 well known cancer therapeutic agents that are selected for their particular usefulness against the condition that is being treated. Included in such combinations of therapeutic agents are combinations of the instant farnesyl-protein transferase inhibitors and an antineoplastic agent. It is also understood 20 that such a combination of antineoplastic agent and inhibitor of farnesyl-protein transferase may be used in conjunction with other methods of treating cancer and/or tumors, including radiation therapy and surgery.

           Examples of an antineoplastic agent include, in 25 general, microtubule-stabilizing agents (such as paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®), epothilone A, epothilone B, desoxyepothilone A, desoxyepothilone B or their derivatives); microtubule-disruptor agents; alkylating agents, anti-metabolites; epidophyllotoxin; an antineoplastic 30 enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes; biological response modifiers and growth inhibitors; hormonal/anti-hormonal therapeutic agents and haematopoietic growth factors.

Example classes of antineoplastic agents include, for example, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the taxanes, the epothilones, discodermolide, the pteridine family of drugs, diynenes and the podophyllotoxins. Particularly useful members of those classes include, for example, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podo-phyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, paclitaxel and the like. Other useful antineoplastic agents include estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons and interleukins.

The preferred class of antineoplastic agents is the taxanes and the preferred antineoplastic agent is paclitaxel.

Radiation therapy, including x-rays or gamma rays which are delivered from either an externally applied beam or by implantation of tiny radioactive sources, may also be used in combination with the instant inhibitor of farnesyl-protein transferase alone to treat cancer.

Additionally, compounds of the instant invention may also be useful as radiation sensitizers, as described in WO 97/38697, published on October 23, 1997, and herein incorporated by reference.

The instant compounds may also be useful in combination with other inhibitors of parts of the signaling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Thus, the instant compounds may be

utilized in combination with a compound which has Raf
antagonist activity. The instant compounds may also be co-
administered with a compounds that is a selective inhibitor of
geranylgeranyl protein transferase type I, a selective inhibitor of
5   farnesyl-protein transferase and/or a compound that is a dual
inhibitor of geranylgeranyl protein transferase type I and
farnesyl-protein transferase. Such a selective inhibitor or dual
inhibitor may be an inhibitor that is competitive with the binding
of the CAAX-containing protein substrate of farnesyl-protein
10   transferase or may be a prenyl pyrophosphate compeptitive
inhibitor.

In particular, the compounds disclosed in the following
patents and publications may be useful as farnesyl
pyrophosphate-competitive inhibitor component of such a
15   composition: U.S. Ser. Nos. 08/254,228 and 08/435,047. Those
patents and publications are incorporated herein by reference.

In practicing methods of this invention, which
comprise administering, simultaneously or sequentially or in any
order, two or more of a protein substrate-competitive inhibitor
20   and a prenyl pyrophosphate-competitive inhibitor, such
administration can be orally or parenterally, including
intravenous, intramuscular, intraperitoneal, subcutaneous, rectal
and topical routes of administration. It is preferred that such
administration be orally. It is more preferred that such
25   administration be orally and simultaneously. When the protein
substrate-competitive inhibitor and prenyl pyrophosphate-
competitive inhibitor are administered sequentially, the
administration of each can be by the same method or by different
methods.

30   The instant compounds may also be useful in
combination with an integrin antagonist for the treatment of
cancer, as described in U.S. Ser. No. 09/055,487, filed April 6, 1998,
which is incorporated herein by reference.

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    As used herein the term an integrin antagonist refers
to compounds which selectively antagonize, inhibit or counteract
binding of a physiological ligand to an integrin(s) that is involved
in the regulation of angiogenisis, or in the growth and

5   invasiveness of tumor cells. In particular, the term refers to
compounds which selectively antagonize, inhibit or counteract
binding of a physiological ligand to the $\alpha v \beta 3$ integrin, which
selectively antagonize, inhibit or counteract binding of a
physiological ligand to the $\alpha v \beta 5$ integrin, which antagonize,

10   inhibit or counteract binding of a physiological ligand to both the
$\alpha v \beta 3$ integrin and the $\alpha v \beta 5$ integrin, or which antagonize, inhibit
or counteract the activity of the particular integrin(s) expressed
on capillary endothelial cells. The term also refers to antagonists
of the $\alpha v \beta 6$, $\alpha v \beta 8$, $\alpha 1 \beta 1$, $\alpha 2 \beta 1$, $\alpha 5 \beta 1$, $\alpha 6 \beta 1$ and $\alpha 6 \beta 4$ integrins. The

15   term also refers to antagonists of any combination of $\alpha v \beta 3$, $\alpha v \beta 5$,
$\alpha v \beta 6$, $\alpha v \beta 8$, $\alpha 1 \beta 1$, $\alpha 2 \beta 1$, $\alpha 5 \beta 1$, $\alpha 6 \beta 1$ and $\alpha 6 \beta 4$ integrins. The instant
compounds may also be useful with other agents that inhibit
angiogenisis and thereby inhibit the growth and invasiveness of
tumor cells, including, but not limited to angiostatin and

20   endostatin.
    Similarly, the instant compounds may be useful in
combination with agents that are effective in the treatment and
prevention of NF-1, restenosis, polycystic kidney disease,
infections of hepatitis delta and related viruses and fungal

25   infections.
    If formulated as a fixed dose, such combination
products employ the combinations of this invention within the
dosage range described below and the other pharmaceutically
active agent(s) within its approved dosage range. Combinations

30   of the instant invention may alternatively be used sequentially
with known pharmaceutically acceptable agent(s) when a
multiple combination formulation is inappropriate.

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EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

EXAMPLE 1

Preparation Of 1-(4-cyanobenzyl)-5-chloromethyl imidazole HCl salt

Step 1:   Preparation of 4-Cyanobenzylamine

Method 1 (Hydrochloride salt): A 72 liter vessel was charged with 190 proof ethanol (14.4 L) followed by the addition of 4-cyanobenzylbromide (2.98 kg) and HMTA (2.18 kg) at ambient temperature. The mixture was heated to about 72-75°C over about 60 min. On warming, the solution thickens and additional ethanol (1.0 liter) was added to facilitate stirring. The batch was aged at about 72-75°C for about 30 min.

The mixture was allowed to cool to about 20°C over about 60 min, and HCl gas (2.20 kg) was sparged into the slurry over about 4 hours during which time the temperature rose to about 65°C. The mixture was heated to about 70-72°C and aged for about 1 hour. The slurry was cooled to about 30°C and ethyl acetate (22.3 L) added over about 30 min. The slurry was cooled to about -5°C over about 40 min and aged at about -3 to about -5°C for about 30 min. The mixture was filtered and the crystalline solid was washed with chilled ethyl acetate (3 x 3 L). The solid was dried under an N_2 stream for about 1 hour before charging to a 50 liter vessel containing water (5.5 L). The pH was adjusted to about 10-10.5 with 50% NaOH (4.0 kg) maintaining the internal temperature below about 30°C. At about 25°C, methylene chloride (2.8 L) was added and stirring continued for about 15 min. The

layers were allowed to settle and the lower organic layer was
removed. The aqueous layer was extracted with methylene
chloride (2 x 2.2 L). The combined organic layers were dried over
potassium carbonate (650 g). The carbonate was removed via
5 filtration and the filtrate concentrated in vacuo at about 25°C to
give a free base as a yellow oil.

  The oil was transferred to a 50 liter vessel with the aid
of ethanol (1.8 L). Ethyl acetate (4.1 L) was added at about 25°C.
The solution was cooled to about 15°C and HCl gas (600 g) was
10 sparged in over about 3 hours, while keeping batch temperature
below about 40°C. At about 20-25°C, ethyl acetate (5.8 L) was
added to the slurry, followed by cooling to about -5°C over about 1
hour. The slurry was aged at about -5°C for about 1 hour and the
solids isolated via filtration. The cake was washed with a chilled
15 mixture of EtOAc/EtOH (9:1 v/v) (1 x 3.8 L), then the cake was
washed with chilled EtOAc (2 x 3.8 L). The solids were dried in
vacuo at about 25°C to provide the above-titled compound.

^{1}H NMR (250 MHz, CDCl$_3$) δ 7.83-7.79 (d, 2H), 7.60-7.57 (d, 2H), 4.79
20 (s, 2H), 4.25 (s, 2H); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 149.9, 139.8,
134.2, 131.2, 119.7, 113.4, 49.9, 49.5, 49.2, 48.8, 48.5, 48.2, 43.8.

  <u>Method 2 (phosphate salt)</u>: A slurry of HMTA in 2.5 L
EtOH was added gradually over about 30 min to about 60 min to a
25 stirred slurry of cyanobenzyl-bromide in 3.5 L EtOH and
maintained at about 48-53°C with heating & cooling in a 22L neck
flask (small exotherm). Then the transfer of HMTA to the reaction
mixture was completed with the use of 1.0 L EtOH. The reaction
mixture was heated to about 68-73°C and aged at about 68-73°C for
30 about 90 min. The reaction mixture was a slurry containing a
granular precipitate which quickly settled when stirring stopped.
  The mixture was cooled to a temperature of about
50°C to about 55°C. Propionic acid was added to the mixture and
the mixture was heated and maintained at a temperature of about

50°C to about 55°C. Phosphoric acid was gradually added over
about 5 min to about 10 min, maintaining the reaction mixture
below about 65°C to form a precipitate-containing mixture. Then
the mixture was gradually warmed to about 65°C to about 70°C

5   over about 30 min and aged at about 65°C to about 70°C for about
30 min. The mixture was then gradually cooled to about 20-25°C
over about 1 hour and aged at about 20-25°C for about 1 hour.

        The reaction slurry was then filtered. The filter cake
was washed four times with EtOH, using the following sequence,

10   2.5 L each time. The filter cake was then washed with water five
times, using 300 mL each time. Finally, the filter cake was washed
twice with MeCN (1.0 L each time) and the above identified
compound was obtained.

15   <u>Step 2:</u>   Preparation of 1-(4-Cyanobenzyl)-2-mercapto-5-
                  <u>hydroxymethylimidazole</u>

        7% water in acetonitrile (50 mL) was added to a 250
mL roundbottom flask. Next, an amine phosphate salt (12.49 g), as
described in Step 1, was added to the flask. Next potassium

20   thiocyanate (6.04 g) and dihydroxyacetone (5.61 g) was added.
Lastly, propionic acid (10.0 mL) was added. Acetonitrile/water
93:7 (25 mL) was used to rinse down the sides of the flask. This
mixture was then heated to 60°C, aged for about 30 minutes and
seeded with 1% thioimidazole. The mixture was then aged for

25   about 1.5 to about 2 hours at 60°C. Next, the mixture was heated
to 70°C, and aged for 2 hours. The temperature of the mixture
was then cooled to room temperature and was aged overnight.
The thioimidazole product was obtained by vacuum filtration.
The filter cake was washed four times acetonitrile (25 mL each

30   time) until the filtrates became nearly colorless. Then the filter
cake was washed three times with water (approximately 25-50 mL
each time) and dried in vacuo to obtain the above-identified
compound.

Step 3:   Preparation of 1-(4-Cyanobenzyl)-5-Hydroxymethylimidazole

A 1L flask with cooling/heating jacket and glass stirrer (Lab-Max) was charged with water (200 mL) at 25°C. The thioimidazole (90.27 g), as described in Step 2, was added, followed by acetic acid (120 mL) and water (50 mL) to form a pale pink slurry. The reaction was warmed to 40°C over 10 minutes. Hydrogen peroxide (90.0 g) was added slowly over 2 hours by automatic pump maintaining a temperature of 35-45°C. The temperature was lowered to 25°C and the solution aged for 1 hour.

The solution was cooled to 20°C and quenched by slowly adding 20% aqueous Na_2SO_3 (25 mL) maintaining the temperature at less than 25°C. The solution was filtered through a bed of DARCO G-60 (9.0 g) over a bed of SolkaFlok (1.9 g) in a sintered glass funnel. The bed was washed with 25 mL of 10% acetic acid in water.

The combined filtrates were cooled to 15 °C and a 25% aqueous ammonia was added over a 30 minute period, maintaining the temperature below 25°C, to a pH of 9.3. The yellowish slurry was aged overnight at 23°C (room temperature). The solids were isolated via vacuum filtration. The cake (100 mL wet volume) was washed with 2 x 250 mL 5% ammonia (25%) in water, followed by 100 mL of ethyl acetate. The wet cake was dried with vacuum/N_2 flow and the above-titled compound was obtained.

^{1}H NMR (250 MHz, CDCl3): δ 7.84-7.72 (d, 2H), 7.31-7.28 (d, 2H), 6.85 (s, 1H), 5.34 (s, 2H), 5.14-5.11 (t, 1H), 4.30-4.28 (d, 2H), 3.35 (s, 1H).

Step 4:   Preparation of 1-(4-cyanobenzyl)-5-chloromethyl imidazole HCl salt

Method 1: 1-(4-Cyanobenzyl)-5-hydroxy-methylimidazole (1.0 kg), as described in above in Step 3, was slurried with DMF (4.8 L) at 22 °C and then cooled to -5°C. Thionyl chloride (390 mL) was added dropwise over 60 min during

which time the reaction temperature rose to a maximum of 9°C.
The solution became nearly homogeneous before the product
began to precipitate from solution. The slurry was warmed to
26°C and aged for 1 h.

5   The slurry was then cooled to 5°C and 2-propanol (120
mL) was added dropwise, followed by the addition of ethyl acetate
(4.8 L). The slurry was aged at 5°C for 1 h before the solids were
isolated and washed with chilled ethyl acetate (3 x 1 L). The
product was dried in vacuo at 40°C overnight to provide the
10   above-titled compound.

^{1}H NMR (250 MHz DMSO-d6): δ 9.44 (s, 1H), 7.89 (d, 2H, 8.3 Hz), 7.89
(s, 1H), 7.55 (d, 2H, 8.3 Hz), 5.70 (s, 2H), 4.93 (s, 2H). ^{13}C NMR (75.5
MHz DMSO-d6): δC 139.7, 137.7, 132.7, 130.1, 128.8, 120.7, 118.4,
15   111.2, 48.9, 33.1.

          Method 2: To an ice cold solution of dry acetonitrile
(3.2 L, 15 L/Kg hydroxymethylimidazole) was added 99% oxalyl
chloride (101 mL, 1.15 mol, 1.15 equiv.), followed by dry DMF (178
20   mL, 2.30 mol, 2.30 equiv.), at which time vigorous evolution of gas
was observed. After stirring for about 5 to 10 min following the
addition of DMF, solid hydroxymethylimidazole (213 g, 1.00 mol),
as described above in Step 3, was added gradually. After the
addition, the internal temperature was allowed to warm to a
25   temperature of about 23°C to about 25°C and stirred for about 1 to
3 hours. The mixture was filtered, then washed with dry
acetonitrile (400 mL displacement wash, 550 mL slurry wash, and
a 400 mL displacement wash). The solid was maintained under a
N_2 atmosphere during the filtration and washing to prevent
30   hydrolysis of the chloride by adventitious H_2O. This yielded the
crystalline form of the chloromethylimidazole hydrochloride.

^{1}H NMR (250 MHz DMSO-d6): δ 9.44 (s, 1H), 7.89 (d, 2H, 8.3 Hz), 7.89
(s, 1H), 7.55 (d, 2H, 8.3 Hz), 5.70 (s, 2H), 4.93 (s, 2H). ^{13}C NMR (75.5

MHz DMSO-d6): δ$_c$ 139.7, 137.7, 132.7, 130.1, 128.8, 120.7, 118.4, 111.2, 48.9, 33.1.

Method 3:   To an ice cold solution of dry DMF (178 mL, 2.30 mol, 2.30 equiv.) in dry acetonitrile (2.56 L, 12 L/Kg Hydroxymethylimidazole) was added oxalyl chloride (101 mL, 1.15 mol, 1.15 equiv). The heterogeneous mixture in the reagent vessel was then transferred to a mixture of hydroxymethylimidazole (213 g, 1.00 mol), as described above in Step 3, in dry acetonitrile (1.7 L, 8 L/Kg hydroxymethylimidazole). Additional dry acetonitrile (1.1 - 2.3 L, 5 - 11 L/Kg hydroxymethylimidazole) was added to the remaining solid Vilsmeier reagent in the reagent vessel. This, now nearly homogenous, solution was transferred to the reaction vessel at T$_i$ ≤ +6°C. The reaction vessel temperature was warmed to a temperature of about 23°C to about 25°C and stirred for about 1 to 3 hours. The mixture was then cooled to 0°C and aged 1 h. The solid was filtered and washed with dry, ice cold acetonitrile (400 mL displacement wash, 550 mL slurry wash, and a 400 mL displacement wash). The solid was maintained under a N$_2$ atmosphere during the filtration and washing to prevent hydrolysis of the chloride by adventitious H$_2$O. This yielded the crystalline form of the chloromethylimidazole hydrochloride.

EXAMPLE 2

1-(4'-Cyanobenzyl) imidazol-5-ylmethyl piperazine

Step 1:   1-(4'-Cyanobenzyl) imidazol-5-ylmethyl piperazine-4-carboxylic acid benzyl ester

        To an acetonitrile solution of 1-(4'-cyanobenzyl)-5-chloromethylimidazole (7.45 mmol) prepared as described in Example 1 and diisopropylethyl amine (22.4 mmol) was added 1-benzyl 1-piperazine carboxylate (10.4mmol). This solution was stirred for 4.0 hour at 80°C. The product was isolated after silica

column purification. ^{1}H-NMR (CDCl$_3$): 7.65 (d, 2H); 7.55 (s, 1H); 7.38 (m, 5H); 7.15 (d, 2H); 7.0 (s, 1H); 5.3 (s, 2H); 5.1 (s, 1H); 3.4 (m, 4H); 3.3 (s, 2H); 2.3 (m, 4H).

5   <u>Step 2:</u>   <u>1-(4'-Cyanobenzyl) imidazol-5-ylmethyl piperazine</u>

The product from Step 1 (6.17 mmol) was dissolved in absolute ethanol followed by the introduction of 10% Pd/C catalyst then hydrogen under atmospheric pressure. The catalyst was removed via filtration through filter-aid and the product was

10   isolated by removing the solvent under reduced pressure. ^{1}H-NMR (CD$_3$OD): 7.8 (s, 1H); 7.75 (d, 2H); 7.3 (d, 2H); 6.9 (s, 1H); 5.45 (s, 2H); 3.3 (m, 4H); 2.6 (s, 2H); 2.3 (m, 4H).

EXAMPLE 3

15   <u>1-(4-Cyanobenzyl)-5-[1-(2-oxo-2-(adamant-1-yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole</u>

   <u>Step 1:</u>   <u>4-Benzyloxycarbonyl-[1-(2-oxo-2-(adamant-1-yl))ethyl]piperazin-2-one</u>

20   To a round bottomed flask were added 4-benzyloxycarbonylpiperazin-2-one (234.26 mg, 1.0 mmol) along with N,N-dimethylforamide(5.0 ml), and sodium hydride (73.0 mg (60%), 1.0 mmol). After the evolution of hydrogen had ceased the reaction was allowed to stir for an additional 30 minutes. To this

25   was added 1 adamantyl bromomethyl ketone(257.18 mg, 1.0 mmol). The reaction stirred at Rt. for 18hrs. The reaction was poured into water(25ml) and extracted with ethylacetate(2X25ml). The ethylacetate layer was washed with brine and dried (MgSO$_4$). Solvent removal yielded 4-benzyloxycarbonyl-[1-(2-oxo-2-

30   (adamant-1-yl)ethyl]piperazin-2-one. 400 Mhz H[1] NMR (CDCl$_3$): 1.68-1.91(m,12H), 2.06 (br s,3H), 3.32(t,2H), 3.77(t,2H), 4.20(s,2H), 4.34(s,2H), 5.16(s,2H), 7.36(m,5H). The material was used with out further purification.

Step 2:   1-[1-(2-oxo-2-(adamant-1-yl))ethyl]piperazin-2-one

4-Benzyloxycarbonyl-[1-(2-oxo-2-(adamant-1-yl))ethyl]piperazin-2-one (389.2 mg, 0.9mmol) was placed it a parr flask along with palladium hydroxide on carbon(50 mg, 20 wt. %) ,

5   Ethanol(75.0ml), Water(5.0 ml), and 2 drops of conc. HCl. The flask was placed on the Parr apparatus and charged with 50 psi of hydrogen. The reaction was allowed to shake for four hours. The reaction was filtered through a celite column and the solvents removed under high vacuum. This resulted in 1-[1-(2-oxo-2-

10   (adamant-1-yl))ethyl]piperazin-2-one. 400 Mhz H^1 NMR (CD$_3$OD): 1.74-1.83(m,6H), 1.91 (br s,6H), 2.05(br s,3H), 3.58(s,4H), 3.90(s,2H), 4.50(s,2H). The material was used with out further purification.

Step 3:   1-(4-Cyanobenzyl)-5-[1-(2-oxo-2-(adamant-1-yl)ethyl)-2-

15   oxo-piperazin-4-yl-methyl]imidazole

1-[1-(2-Oxo-2-(adamant-1-yl))ethyl]piperazin-2-one (253.4 mg, 0.81 mmol) was placed into a round bottomed flask and diisopropylethylamine (0.71ml), acetonitrile (20.0ml) and 1-(4-cyanobenzyl-5-chloromethyl)imidazole hydrochloride (prepared

20   as described in Example 1) (217.2 mg, 0.81 mmol). The reaction was heated at reflux for 3 hours. The excess acetonitrile was removed under vacuum and the residue dissolved into ethylacetate(25.0ml). The ethylacetate layer was washed with water and the aqueous layer back extracted with additional

25   ethylacetate(15.0ml). The combined ethylacetate extracts were dried(MgSO$_4$). Solvent removal yielded 249.0 mg (65%) of a yellow foam. The foam was dissolved in to 1.0N HCl and washed with hexane/ethylacetate 25 ml (75/25). The aqueous layer was then basified with ammonium hydroxide and the aqueous layer

30   reextracted with ethylacetate. The organic layer was again dried(MgSO$_4$) and solvent removed. The residue was treated with a dioxane/methanol/HCl solution which gave, after lyophlizing, 1-(4-Cyanobenzyl-5-[1-(2-oxo-2-(adamant-1-yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole dihydrochloride.   400 Mhz H^1 NMR (CDCl$_3$):

1.55-1.75(m,12H), 2.01(br s,3H), 2.40-2.61(m,2H), 3.06-3.19(m,5H),
3.32(s,2H), 3.71-3.75(d,1H), 5.29(s,2H), 7.02(s,1H), 7.14(d,2H),
7.58(s,1H), 7.64(d,2H)

5   **EXAMPLE 4**

R/S 1-(4-Cyanobenzyl)-5-[1-(2-hydroxy-2-(adamant-1-yl)ethyl)-2-
oxo-piperazin-4-yl-methyl]imidazole

10   A solution of 201 mg (.4 mmol) of 1-(4-cyanobenzyl-5-[1-
(2-oxo-2-(adamant-1-yl)ethyl)-2-oxo-piperazin-4-yl-methyl]-
imidazole (prepared as described in Example 3), 138.0 mg (1.0
mmol) sodium carbonate in methanol 10ml was treated with
sodium borohydride (22.6 mg, 0.60 mmol) at 0°C. The reaction was
15   allowed to warm to Rt. The reaction was diluted with water/Brine
and the reaction extracted with ethyl acetate. The ethylacetate
layer was washed with water/brine and dried (MgSO$_4$). Solvent
removal yielded 189.0 mg of a solid. The solid was flashed through
a small silica column eluting with methanol/chloroform (10/90).
20   This resulted in R/S 1-(4-Cyanobenzyl-5-[1-(2-hydroxy-2-(adamant-
1-yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole. 400 Mhz H^1
NMR (CDCl$_3$): 1.55-1.75(m,12H), 2.01(br s,3H), 2.40-2.61(m,2H), 3.06-
3.19(m,5H), 3.32(s,2H), 3.71-3.75(d,1H), 5.29(s,2H), 702(s,1H),
7.14(d,2H), 7.58(s,1H), 7.64(d,2H). High Res. FAB MS: Theoretical
25   Mass 474.2864, Measured Mass 474.2864 (C$_{28}$H$_{35}$N$_5$O$_2$+H$^+$)

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EXAMPLE 5

5   1-(4-Cyanobenzyl)-5-[1-(2-hydroxy-2-(adamant-1-yl)ethyl)-2-oxo-
piperazin-4-yl-methyl]imidazole (Isomer I) and
1-(4-Cyanobenzyl)-5-[1-(2-hydroxy-2-(adamant-1-yl)ethyl)-2-oxo-
piperazin-4-yl-methyl]imidazole (Isomer II)

R/S 1-(4-Cyanobenzyl-5-[1-(2-hydroxy-2-(adamant-1-
10   yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole (prepared as
described in Example 3), 50.0mg(0.1mmol) was put through a
Chiralpack AD column eluting with hexane/ethanol (35/65) Flow
Rate 7.0ml/min. The first fraction off was concentrated under
high vac to give a glass. The glass was dissolved into dioxane
15   and 2 drops of 1.0N HCl in dioxane added. The solution was
lyophilized to give a white solid (Isomer I). High Res. FAB MS:
Theoretical Mass 474.2863, Measured Mass 474.2871
$(C_{28}H_{35}N_5O_2+H^+)$.

20   The second fraction off the above column was processed as above
to give a white solid (Isomer II). High Res. FAB MS: Theoretical
Mass 474.2863, Measured Mass 474.2861 $(C_{28}H_{35}N_5O_2+H^+)$

EXAMPLE 6

25

1-(4-Cyanobenzyl)-5-[1-(2-acetyloxy-2-(adamant-1-yl)ethyl)-2-oxo-
piperazin-4-yl-methyl]imidazole

R/S 1-(4-Cyanobenzyl-5-[1-(2-hydroxy-2-(adamant-1-
30   yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole (92.0mg,0.2mmol)
was dissolved into pyridine (1.0ml) and the solution cooled to 5°C
(ice/water). To this solution was added aceticanhydride
(20ul,0.2mmol). The reaction was allowed to warm to room
temperature. The solvent was removed under vac and the residue

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dissolved into ethyl acetate (10ml), washed with water (1x1.0ml), brine(1x,1.0ml), and dried (MgSO$_4$). Solvent removal yielded a tan solid (105.0mg). The solid was purified on a prep column (Waters C18). Lyophilizing resulted in a white solid. 400 Mhz H^1 NMR (CD$_3$OD): 1.64(br s,6H), 1.74(q,6H), 1.99(br s,3H), 2.02(s,3H), 2.60(m,2H), 2.91(dd,2H), 3.03-3.09(m,1H), 3.27(d,1H), 3.39(d,1H), 3.54(dd,2H), 3.65(dd,1H), 4.75(d,1H), 5.65(s,2H), 7.44(d,2H), 7.62(s,1H)7.78(d,2H), 9.09(s,1H). High Res. FAB MS: Theoretical Mass 516.2969 , Measured Mass 516.2989(C$_{30}$H$_{37}$N$_5$O$_3$+H$^+$)

EXAMPLE 7

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl] piperazine-4-(N-1-adamantyl)carboxamide

To 1-(4'-cyanobenzyl) imidazol-5-ylmethyl piperazine Example 2, step 2 (0.445 mmol) in ethyl acetate and methanol was added the commercially available 1-adamantyl isocyanate (0.423 mmol) and diisopropylethyl amine (0.89 mmol). After stirring for 18 hours the reaction was purified via preparative hplc and the title compound was then isolated via lyophilization. FAB-MS: calc: 458.6 found: 459.6. ^{1}H-NMR (CD$_3$OD): 9.1ppm (s, 1H); 7.85ppm (d, 2H); 7.6ppm (s, 1H); 7.45ppm (d, 2H); 5.7ppm (s, 2H); 3.55ppm (s, 2H); 3.2ppm (m, 4H); 2.4ppm (m, 4H); 2.1ppm (m, 9H); 1.7ppm (s, 6H).

EXAMPLE 8

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-(N-1-adamantyl)carbonyl piperazine

Step 1:   1-(N-boc)-4-(N-1-adamantyl)carbonyl piperazine
Commercially available 1-boc-piperazine (10 mmol) and 1-adamantane carbonyl chloride (10 mmol) were dissolved in

chloroform (50mL) and DIEA (22 mmol) and stirred for 18 hours. The reaction was then diluted with chloroform and washed with dilute potassium hydrogen sulfate, dilute sodium bicarbonate and saturated sodium chloride solutions. The organic layer was dried

5   with sodium sulfate and evaporated to prrovide the title compound. ^{1}H-NMR (CDCl$_3$): 3.65ppm (m, 4H); 3.4ppm (m, 4H); 2.1ppm (s, 3H); 2.0ppm (s, 6H); 1.7ppm (s, 6H); 1.4ppm (s, 9H).

Step 2:   1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-(N-1-
10   adamantyl)carbonyl piperazine
            The product from Step 1 was treated with neat trifluoroacetic acid and the desired product was isolated as a free base compound after partitioning between methylene chloride and sodium carbonate. This product (0.373 mmol) was then added

15   to a solution of 1-(4'-cyanobenzyl)-5-chloromethylimidazole (1, 0.373 mmol), prepared as described in Example 1, in acetonitrile and DIEA (0.746 mmol) and stirred for 3 hours at 80°C. The product was purified via preperative hplc and the title compound isolated via lyophilization. FAB-MS: calc: 443.6 found: 444.3. ^{1}H-

20   NMR (CD$_3$OD): 9.1ppm (s, 1H); 7.8ppm (d, 2H); 7.6ppm (s, 1H); 7.5ppm (d, 2H); 5.7ppm (s, 2H); 3.5ppm (m, 6H); 2.4ppm (m, 4H); 2.05ppm (s, 3H); 2.0ppm (s, 6H); 1.8ppm (s, 6H).

EXAMPLE 9

25

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-[N-(1R)-(-)-10-camphorsulfonyl]piperazine

Step 1:   1-(4'-Cyanobenzyl) imidazol-5-ylmethyl-4-[N-(1R)-(-)-10-
30   camphorsulfonyl]piperazine
            The commercially available (1R)-(-)-10-camphor-sulfonyl chloride (45, 0.359 mmol) and 1-(4'-Cyanobenzyl) imidazol-5-ylmethyl piperazineprepared as described in Example 2 (0.342 mmol) were dissoloved in ethyl acetate and DIEA (0.684 mmol)

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and stirred for 18 hours at 25°C. The product was purified via preperative hplc and the title compound was isolated via lyophilization. FAB-MS: calc: 495.6 found: 496.3. ^{1}H-NMR (CD$_3$OD): 9.1ppm (s, 1H); 7.9ppm (d, 2H); 7.7ppm (s, 1H); 7.5ppm (d, 2H); 5.7ppm (s, 2H); 3.6ppm (s, 2H); 3.1ppm (d, 1H); 3.2ppm (m, 4H); 2.8ppm (d, 1H); 2.4ppm (m, 4H); 2.1ppm (m, 3H); 1.6ppm (m, 1H); 1.5ppm (m, 1H); 1.1ppm (s, 3H); 0.9ppm (s, 3H).

EXAMPLE 10

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-(1-adamantylmethyl) piperazine

Step 1:   1-(N-1-adamantyl)methyl piperazine

1-(N-boc)-4-(N-1-adamantyl)carbonyl piperazine (2.98 mmol), prepared as described in Example 8, Step 1, was treated with neat trifluoroacetic acid and the intermediate was isolated as a free base compound after partitioning between methylene chloride and sodium carbonate and then reduced with lithium aluminum hydride (5.96 mmol) in refluxing THF for 18 hours and then worked up as specified in Fieser and Fieser, 1967, 1, 584, to provide the titled compound. FAB-MS: calc: 234.6 found: 235.1. ^{1}H-NMR (CDCl$_3$): 2.8ppm (m, 4H); 2.45ppm (m, 4H); 2.0ppm (m, 5H); 1.8-1.5ppm (m, 12H).

Step 2:   1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-(1-adamantylmethyl) piperazine

The product from Step 1 (0.812 mmol) was then added to a solution of 1-(4'-cyanobenzyl)-5-chloromethylimidazole (0.812 mmol), prepared as described in Example 1, in acetonitrile and DIEA (1.62 mmol) and stirred for 3 hours at 80°C. The product was purified via preperative hplc and the titled compound was isolated via lyophilization. FAB-MS: calc: 429.5 found: 430.2. ^{1}H-NMR (CD$_3$OD): 8.3ppm (s, 1H); 7.8ppm (d, 2H); 7.4ppm (d, 2H);

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7.3ppm (s, 1H); 5.6ppm (s, 2H); 3.5ppm (s, 2H); 2.5-2.9ppm (m, 10H); 2.05ppm (m, 3H); 1.7-1.9ppm (m, 12H).

EXAMPLE 11:

5

1-(4-Cyanobenzyl)-5-[1-(2-(adamant-1-yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole

Step 1:   1-Bromo-2-(adamant-1-yl)ethane

10   1-Hydroxy-2-(adamant-1-yl)ethane (901.0mg, 5.0mmol) was treated with phosphorus pentabromide(3.0gm, 7.0mmol) in diethyl ether and warmed slightly until a noticeable exotherm was observed. The resulting red solution was washed with aqueous sodium bicarbonate solution and dried (Na$_2$SO$_4$). Solvent

15   removal gave crude 1-Bromo-2-(adamant-1-yl)ethane. The material was used as is without further purification.

Step 2:   4-Benzyloxycarbonyl-[1-(2-(adamant-1-yl))ethyl]piperazin-2-one

20   4-Benzyloxycarbonylpiperazin-2-one (1.17g, 5.0mmol) was dissolved in to dry dimethylforamide and sodium hydride (220mg, 5.5mmol) added. After the evolution of hydrogen had stopped the 1-Bromo-2-(adamant-1-yl)ethane, prepared as described in Step 1, was added and the reaction heated at 80°C for

25   8 hours. The reaction was diluted with water and extracted with methylene chloride. The methylene chloride layer was dried(MgSO$_4$), and solvent removed to yield a gum. The gum was dissolved into n-butylchloride and flashed through a short silica column. This resulted the title 4-Benzyloxycarbonyl-[1-(2-

30   (adamant-1-yl))ethyl]piperazin-2-one. 400 Mhz H^1 NMR (CDCl$_3$): 1.24-1.36(m, 2H), 1.52(s,6H), 1.61-1.77(m,6H), 1.95(br s,3H), 3.10(br s, 2H), 3.69(t,2H), 4.12(s,2H), 5.15(d,2H), 7.35-7.38(m,5H). High res. ES MS: Theoretical Mass 397.2486, Measured Mass 397.2502 (C$_{24}$H$_{32}$N$_2$O$_3$+H$^+$)

Step 3:   1-[(2-(adamant-1-yl))ethyl]piperazin-2-one

4-Benzyloxycarbonyl-[1-(2-(adamant-1-
yl))ethyl]piperazin-2-one (570.0mg, 1.44mmol), prepared as
5   described in Step 2, was added to a flask containing
ethanol(15.0ml), water(1.0ml), conc. hydrochloric acid(2 drops,
and palladium hydroxide(20% by Wt., 50.0mg). The flask was
hydrogenated for 3.5 hours. The reaction was filtered through
celite and the solvents removed to give 1-[(2-(adamant-1-
10   yl))ethyl]piperazin-2-one as the hydrochloride salt. 400 Mhz H^1
NMR (CD$_3$OD): 1.33-1.37(m, 2H), 1.58(s,6H), 1.73(q, 6H), 3.45-
3.53(m,4H), 3.61(t, 2H), 3.80(s,2H). High res. FAB MS: Theoretical
Mass 263.2118, Measured Mass 263.2122(C$_{16}$H$_{26}$N$_2$O+H$^+$)

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15   **Step 4:**   1-(4-Cyanobenzyl)-5-[1-(2-(adamant-1-yl)ethyl)-2-oxo-
piperazin-4-yl-methyl]imidazole

1-[(2-(adamant-1-yl))ethyl]piperazin-2-one
hydrochloride (400.0mg, 1.34mmol), prepared as described in Step
3, along with 1-(4-cyanobenzyl-5-chloromethyl)imidazole
20   hydrochloride (360.0mg, 1.34mmol), prepared as described in
Example 1, acetonitrile(20.0ml), and diisopropylethylamine
(1.40ml, 8.0mmol) were heated at reflux for eight hours. The
acetonitrile was removed under vacuum and the residue
dissolved in ethyl acetate(50.0ml). The ethyl acetate solution was
25   washed with water (2x,10.0ml), brine(25.0ml), and dried(MgSO$_4$).
The solvents were removed under high vac. The resulting gum
purified using a silica column eluting with methanol/chloroform
(10/90). The isolated free base was dissolved into HCl/dioxane
(0.1N, 2.0ml) and lyophilized to give 1-(4-Cyanobenzyl-5-[1-(2-
30   (adamant-1-yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole as the
dihydrochloride salt.. 400 Mhz H^1 NMR (CDCl$_3$) (Free Base): 1.22-
1.26(m, 2H), 1.53(s,6H), 1.67(q, 6H), 1.95(br s,3H), 2.52(t, 2H),
3.03(s,2H), 3.05(t,2H), 3.30(s, 2H), 3.31-3.35(m, 2H), 5.29(s, 2H), 7.02(s,

1H), 7.13(d, 2H), 7.57(s, 1H), 7.63(d,2H). High res. FAB MS:
Theoretical Mass 458.2914, Measured Mass 458.2911($C_{28}H_{35}N_5O+H^+$)

EXAMPLE 12

5

1-(4-Cyanobenzyl)-5-[1-(1-(adamant-1-yl)methyl)-2-oxo-piperazin-4-
yl-methyl]imidazole

Step 1: N^1-tert-butylcarboxy-[N^2-(adamant-1-yl)methyl)]-1,2-
10   ethanediamine
               Boc-aminoacetaldehyde (1.0g, 6.10mmol) along with 1-
adamantanemethylamine(1.0g, 6.10), and methanol(50.0ml) were
combined in a round bottom flask. The reaction was cooled to 5°C
in an ice/water bath, purged with argon and sodium acetate(1.0g,
15   12.20mmol) added portion wise. Palladium on activated
carbon(50.0mg, Palladium content 10%) was added, the flask
charged with hydrogen, and the ice bath removed. The reaction
was allowed to run over night. The reaction was purged with
argon and filtered through celite. The solvents were removed and
20   the resulting gum dissolved in ethyl acetate(100.0ml). The ethyl
acetate solution was extracted with dilute citric acid(2x50.0ml).
The combined citric acid extract was washed with additional
ethyl acetate(2x25ml). The citric acid solution was then basified
using conc. ammonium hydroxide and extracted with
25   chloroform(2x50ml). The chloroform extract was washed with
brine(25.0ml) and dried(MgSO$_4$). Solvent removal under high vac
resulted in N^1-tert-butylcarboxy-[N^2-(adamant-1-yl)methyl)]-1,2-
ethanediamine. 400 Mhz H^1 NMR (CDCl$_3$) (Free Base): 1.45(s, 9H),
1.51(s,6H), 1.68(q, 6H), 1.96(br s,3H), 2.22(s, 2H), 2.70(t, 2H),
30   3.20(m,2H). High res. FAB MS: Theoretical Mass 309.2536,
Measured Mass 309.2535($C_{18}H_{32}N_2O_2+H^+$)

Step 2: N^1-tert-butylcarboxy[N^2-(adamant-1-yl)methyl)]-N^2-(2-
               bromoacetyl)-1,2-ethanediamine

N^1-tert-butylcarboxy-[N^2-(adamant-1-yl)methyl)]-1,2-ethanediamine (1.20g, 3.90mmol), prepared as described in Step 1, was placed in a round bottom flask and ethyl acetate added(50.0ml), saturated sodium carbonate solution(25.0ml), and

5   water(25.0ml). The reaction was cooled to 5°C (ice/water) and bromoacetylbromide added in small portions until no starting material remained(TLC, 95/5, Chloroform/methanol, I$_2$ stain). The reaction was allowed to warm to room temperature and transferred to a separatory funnel where the mixture was shaken

10   several separate times until the ph of the ethyl acetate layer remained basic. Additional ethyl acetate was added(50.0ml) and the layers were separated. The organic layer washed with dilute citric acid solution(1x25.0ml), saturated sodium bicarbonate(1x25.0ml), water(1x25.0ml), brine(1x25.0ml), and

15   dried(MgSO$_4$). Solvent removal gave N^1-tert-butylcarboxy[N^2-(adamant-1-yl)methyl)]-N^2-(2-bromoacetyl)-1,2-ethanediamine. 400 Mhz H^1 NMR (CDCl$_3$): 1.45(s, 9H), 1.5(d,5H), 1.61-1.74(, 7H), 1.91(d,3H), 3.08(s, 2H), 3.23-3.39(m, 2H), 3.50-3.54(m,2H), 3.93(s,2H). High res. FAB MS: Theoretical Mass 429.1747, Measured Mass

20   429.1737(C$_{20}$H$_{33}$BrN$_2$O$_3$+H$^+$)

Step 3:   4-Benzyloxycarbonyl-[1-((adamant-1-yl)methyl)]piperazin-2-one

N^1-tert-Butylcarboxy[N^2-(adamant-1-yl)methyl)]-N^2-(2-

25   bromoacetyl)-1,2-ethanediamine(1.41g,3.3mmol), prepared as described in Step 2, was added to a reaction flask containing dimethylforamide (25.0ml), and Cesium carbonate(6.42g, 19.7mmol). The reaction was heated at 100°C for ten hours. The reaction was diluted water/brine (50:50, 50.0ml) and extracted

30   with ethyl acetate(2x50.0ml). The ethyl acetate layer was then washed with dilute citric acid solution(25.0ml), saturated sodium bicarbonate solution(25.0ml), brine(25.0ml), and dried(MgSO$_4$). Solvent removal gave 4-Benzyloxycarbonyl-[1-((adamant-1-yl)methyl)]piperazin-2-one.400 Mhz H^1 NMR (CDCl$_3$): 1.48(s, 9H),

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1.52(s,6H), 1.67(q, 6H), 1.97(br s,3H), 3.10(s, 2H), 3.39-3.43(m, 2H), 3.60(t,2H), 4.07(s,2H). High res. FAB MS: Theoretical Mass 349.2486, Measured Mass 349.2479($C_{20}H_{32}N_2O_3$+H^+).

5   Step 4:   [1-((adamant-1-yl)methyl)]piperazin-2-one

4-Benzyloxycarbonyl-[1-((adamant-1-yl)methyl)]-piperazin-2-one (300.0mg, 0.9mmol), prepared as described in Step 3, was dissolved into neat trifluoroacetic acid(5.0ml) and the reaction allowed to stir for 30 minutes. Excess trifluoroacetic 10   acid was removed under high vacuum and the resulting gum treated with 4.0N HCl in dioxane and after 10 minutes excess solvents were removed under high vacuum to give 1-((adamant-1-yl)methyl)piperazin-2-one as the hydrochloride salt. 400 Mhz H^1 NMR (CD$_3$OD) : 1.62(s, 6H),1.68-1.77 (m,6H), 1.97(br s,3H), 3.16(s, 15   2H), 3.52(t, 2H), 3.72(t,2H), 3.86(s, 2H). High res. FAB MS: Theoretical Mass 249.1961, Measured Mass 249.1952($C_{15}H_{24}N_2O$+H^+).

Step 5:   1-(4-Cyanobenzyl)-5-[1-(1-(adamant-1-yl)methyl)-2-oxo-
20   piperazin-4-yl-methyl]imidazole

1-(4-cyanobenzyl-5-chloromethyl)imidazole hydrochloride(268.0mg, 1.0mmol), prepared as described in Example 1, was added to a reaction flask along with aceto-nitrile(25.0ml), diisopropylethylamine(1.0ml, 6.0mmol) and 1-25   ((adamant-1-yl)methyl)piperazin-2-one(275.0mg, 1.0mmol) prepared as described in Step 4. The reaction was heated at 80°C for 10 hours. The acetonitrile was removed under high vacuum to give 542.0mg of a foam. The foam was dissolved into ethyl acetate(50.0ml) and washed with dilute ammonium hydroxide 30   solution(2x25.0ml). The organic layer was washed with brine(25.0ml), and dried(MgSO$_4$). Solvent removal gave 382.0mg of a foam which was flashed through a silica column eluting with methanol/chloroform (5/95) to give 1-(4-Cyanobenzyl-5-[1-(1-(adamant-1-yl)methyl)-2-oxo-piperazin-4-yl-methyl]imidazole as

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the free base. The free base was dissolved into 4.0N dioxane and the solvents removed under high vacuum to give the title compound as the dihydrochloride salt. 400 Mhz H^1 NMR (CDCl$_3$) (Free Base): 1.52(s, 6H), 1.65(q, 6H), 1.96(s, 3H), 2.53(t, 2H), 3.00(s, 2H), 3.09(s, 2H), 3.18(t, 2H), 3.32(s, 2H), 5.31(s, 2H), 7.01(s, 1H), 7.14(d, 2H), 7.56(s, 1H), 7.63(d, 2H). High res. FAB MS: Theoretical Mass 444.2758, Measured Mass 444.2757($C_{27}H_{33}N_5O$+H$^+$)

EXAMPLE 13

1-(4'-Cyanobenzyl)-2-methyl-imidazol-5-ylmethyl piperazine-4-(N-1-adamantyl)carboxamide

Step 1:   Preparation of 1-(4-Cyanobenzyl)-2-methylimidazole-5-carboxaldehyde

      Step A: Preparation of 4-Bromo-2-methylimidazole-5-carboxaldehyde

4-Bromo-5-hydroxymethyl-2-methylimidazole was prepared according to the procedure described by S. P. Watson, Synthetic Communications, 22, 2971-2977 (1992). A solution of 4-bromo-5-hydroxymethyl-2-methylimidazole (4.18 g, 21.9 mmol) was refluxed with manganese dioxide (16.1 g) in 1:1 methylene chloride:dioxane (200 mL) for 16 h. The cooled reaction was filtered through celite and concentrated to yield the title compound as a pale yellow solid.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 9.57 (1H, s), 2.52 (3H, s).

      Step B: 4-Bromo-1-(4-cyanobenzyl)-2-methylimidazole-5-carboxaldehyde

4-Cyanobenzylbromide (1.05 g, 5.39 mmol) was added to a solution of 4-bromo-2-methylimidazole-5-carboxaldehyde (1.02

g, 5.39 mmol) (Step A) in dimethylacetamide (15 mL). The solution
was cooled to -10°C and powdered potassium carbonate (0.745 g,
5.39 mmol) added. The reaction was stirred at -10°C for 2 h, and a
further 4 h at 20°C. The reaction was diluted with water and
5   extracted with ethyl acetate. The organic phase was washed with
water, saturated brine, and dried over magnesium sulfate.
Solvent evaporation yielded a white solid.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 9.68 (1H, s), 7.64 (2H, d, J=7 Hz) , 7.15
10   (2H, d, J=7Hz), 5.59 (2H, s), 2.40 (3H, s).

Step C: 1-(4-Cyanobenzyl)-2-methylimidazole-5-
               carboxaldehyde

15   A solution of 4-bromo-1-(4-cyanobenzyl)-2-
methylimidazole-5-carboxaldehyde (1.33 g, 4.37 mmol) (Step B)
and imidazole (0.600 g, 8.74 mmol) in 1:1 ethyl acetate-alcohol (150
mL) was stirred with 10% palladium on carbon (0.020 g) under 1
atm hydrogen. After 2 h, the reaction was filtered through celite
20   and concentrated to give the title compound as a white solid.

^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 9.62 (1 H, s), 7.90 (1H, s), 7.81 (2H,
d, J=8 Hz), 7.20 (2H, d, J=8 Hz), 5.64 (2H, s), 2.33 (3H, s).
Step 2:   1-[1-(4-cyanobenzyl)-2-methylimidazol-5-ylmethyl]-4-
25   piperazine

           A mixture of 2.50 g (11.05 mmol) of 1-(4-cyanobenzyl)-2-
methylimidazole-5-carboxaldehyde (prepared as described in Step
1), 2.44 g (11.05 mmol) of 1-(benzyloxycarbonyl)piperazine, and
30   4.11 ml (13.81 mmol) of titanium isopropoxide in 5 ml anh. THF
was stirred at RT for 1h. The reaction was diluted with 5 ml of
anh. EtOH, and the solution treated with 695 mg(11.05 mmol) of
sodium cyanoborohydride. The reaction was heated at 65°C for
1h, and was stirred at RT for an additional 18h. The reaction was

poured into excess water, and the suspension stirred vigorously
for 10 min. The mixture was diluted with ethyl acetate, and was
filtered through a Celite pad. The filtrate was separated, and the
organic layer dried and concentrated in vacuo to give a brown oil.

5   The oil was purified by column chromatography over silica gel
using acetonitrile followed by 5% methanol/chloroform to give 2 g
of a yellow oil. The oil was dissolved in 15 ml abs. Ethanol, and
was hydrogenated at atmospheric pressure over 250 mg of 10% Pd
on C catalyst. After approx. 30 h, the reaction was filtered

10   through a celite pad to give the desired product as a pale yellow
oil. H1 NMR(CDCl₃): 2.29(s,3H), 2.30(br s, 4H), 2.90(br s, 4H),
3.29(s,2H), 5.14(s,2H), 6.87(s,1H), 7.05(d,2H), 7.62(d,2H).

Step 3:   1-(4'-Cyanobenzyl)-2-methyl-imidazol-5-ylmethyl
15   piperazine-4-(N-1-adamantyl)carboxamide   (68)
To 1-(4'-Cyanobenzyl)-2-methyl-imidazol-5-ylmethyl
piperazine (prepared as described in Step 2) (0.254 mmol) in
methylene chloride was added the commercially available 1-
adamantyl isocyanate (0.254 mmol) and diisopropylethyl amine

20   (0.508 mmol). After stirring for 1 hour the reaction was
evaporated and purified via preparative hplc and isolated via
lyophilization. HI-RES MS: calc: 473.3023 found: 473.3034. ¹H-
NMR (CD₃OD): 7.75ppm (d, 2H); 7.3ppm (m, 3H); 5.55ppm (s, 2H);
3.35ppm (s, 2H); 3.1ppm (m, 4H); 2.5ppm (s, 3H); 2.35ppm (m, 4H);

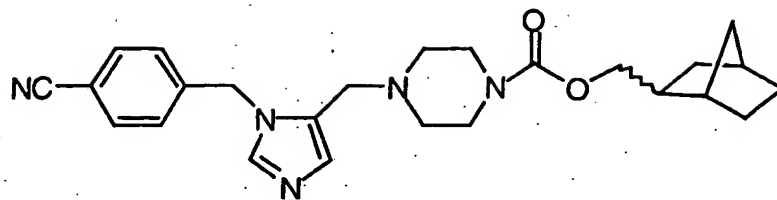25   2.05ppm (s, 3H); 2.0ppm (s, 6H), 1.65ppm (s, 6H).

EXAMPLE 14

### Preparation of Carbamates from Alcohols

30

To each of 14 previously tared screw cap test tubes
was added approximately 1.25 equivalents of one of the 14
alcohols. After determining the weights of alcohols by difference
the appropriate amount of p-nitrophenyl chloroformate (1.27

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equivalents) was added to each of the tubes as a freshly made
tetrahydrofuran:acetonitrile (7:1) solution. This was stirred for 10
minutes and then pyridine (1.37 equivalents) was added to each
tube followed by stirring for 1.5 hours. Each tube was diluted

5   with 1.5mL each of ethyl acetate and water. The aqueous was
removed and the organic layer was rotary speed evaporated to a
pellet. To each of the 14 tubes was added 1.0 mL of ethyl
acetate:DCM:methanol (1:1:0.1) and 0.1 mmol of a stock DMF
solution of 1-(4'-Cyanobenzyl) imidazol-5-ylmethyl piperazine,

10   prepared as described in Example 2 and 0.2 mmol DIEA. Stir for
18 hours. To each tube was added 1.0 mL of ethyl acetate then
each tube was washed with 5x1mL of 1.0N NaOH. The organic
layer was then rotary speed evaporated to a pellet. The resulting
pellet was dissolved in 2.0 mL of DMSO and submitted for LC and

15   HI-RES Mass spec analysis. The completeness of reaction was
estimated by comparing the AUC of each reaction against an
independently prepared standard of known concentration that
was also prepared in the library run.

The following compounds of the invention were

20   prepared by this method:

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl] piperazine-
4-carboxylic acid (2-norbornane)methyl ester
Hi-Res MS: calc: 434.2530 found: 434.2550
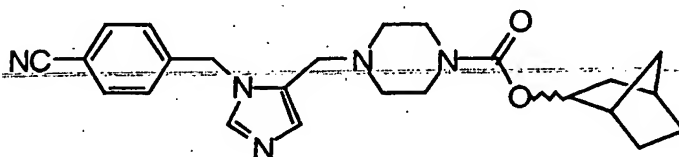
1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-piperazine-
4-carboxylic acid (2-norbornane)methyl ester
Hi-Res MS: calc: 420.2390 found: 420.2394

EXAMPLE 15

5   **Preparation of Amides from Acids**

        To each of twelve previously tared screw cap test
tubes was added approximately 0.12 mmol of a multicyclic
containing carboxylic acid acids. After determining this weight
10   by difference, a DCM solution of 2,3-dimethyl-2-fluoro-pyridinium
tosylate (1.2 equivalents vs. acid, 218 mg/mL) was added to each
tube and then a DCM solution of triethyl amine (1.2 equivalents
vs. acid, 250 uL/mL DCM) was added. These solutions were stirred
for 15 minutes and then a solution of 1-(4'-cyanobenzyl) imidazol-
15   5-ylmethyl piperazine (0.1 mmol in DMF), prepared as described

in Example 2, and DIEA (0.2 mmol) in DCM (0.5 mL) for a total
volume of 0.615 mL was added to each tube and then stirred for 5
hours. Each tube was washed with 2x1 mL of 1% trifluoroacetic
acid. The DCM layers were removed and then transferred to new

5   pre-tared test tubes and then rotary speed evaporated to a pellet.
The resulting pellet was dissolved in 2.0 mL of DMSO and
submitted for LC and HI-RES Mass spec analysis. The
completeness of reaction was estimated by comparing the AUC of
each reaction against an independently prepared standard of

10   known concentration that was also prepared in the library run.
       The following compounds of the invention were
prepared by this method:
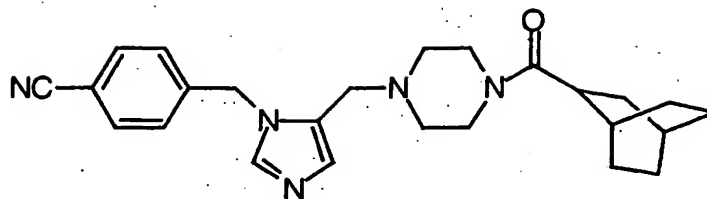
1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl] piperazine-
4-(2-bicyclo-[2.2.2]-octylcarbonyl)
Hi-Res MS: calc: 418.2613   found: 418.2601
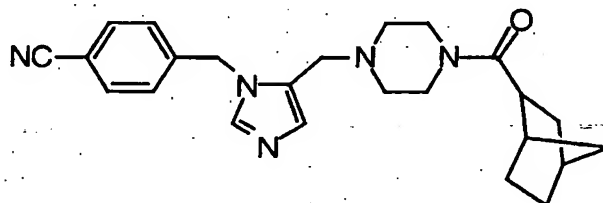
1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-piperazine-
4-(2-norbornanecarbonyl)
Hi-Res MS: calc: 404.2461   found: 404.2445

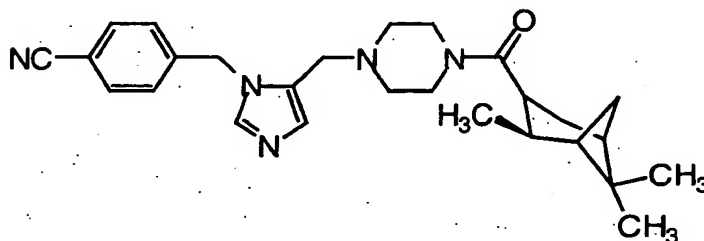1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-
4-cis/trans-(2,6,6-trimethylbicyclo[3.1.1]heptanecarbonyl)-
piperazine
Hi-Res MS: calc: 446.291 found: 446.2914

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EXAMPLE 16

In vitro inhibition of ras farnesyl transferase

5   Transferase Assays. Isoprenyl-protein transferase activity assays are carried out at 30°C unless noted otherwise. A typical reaction contains (in a final volume of 50 μL): [^{3}H]farnesyl diphosphate, Ras protein , 50 mM HEPES, pH 7.5, 5 mM MgCl$_2$, 5 mM dithiothreitol, 10 μM ZnCl$_2$, 0.1% polyethyleneglycol (PEG)

10   (15,000-20,000 mw) and isoprenyl-protein transferase. The FPTase employed in the assay is prepared by recombinant expression as described in Omer, C.A., Kral, A.M., Diehl, R.E., Prendergast, G.C., Powers, S., Allen, C.M., Gibbs, J.B. and Kohl, N.E. (1993) Biochemistry 32:5167-5176. After thermally pre-equilibrating the

15   assay mixture in the absence of enzyme, reactions are initiated by the addition of isoprenyl-protein transferase and stopped at timed intervals (typically 15 min) by the addition of 1 M HCl in ethanol (1 mL). The quenched reactions are allowed to stand for 15 m (to complete the precipitation process). After adding 2 mL of 100%

20   ethanol, the reactions are vacuum-filtered through Whatman GF/C filters. Filters are washed four times with 2 mL aliquots of 100% ethanol, mixed with scintillation fluid (10 mL) and then counted in a Beckman LS3801 scintillation counter.

          For inhibition studies, assays are run as described

25   above, except inhibitors are prepared as concentrated solutions in 100% dimethyl sulfoxide and then diluted 20-fold into the enzyme assay mixture. Substrate concentrations for inhibitor IC$_{50}$ determinations are as follows: FTase, 650 nM Ras-CVLS (SEQ.ID.NO.: 1), 100 nM farnesyl diphosphate.

30   The compounds of the instant invention described in the above Examples 3-15 were tested for inhibitory activity against human FPTase by the assay described above and were found to have IC$_{50}$ of ≤5 μM.

EXAMPLE 17

ModifiedIn vitro GGTase inhibition assay

5

        The modified geranylgeranyl-protein transferase inhibition assay is carried out at room temperature. A typical reaction contains (in a final volume of 50 μL): [^{3}H]geranylgeranyl diphosphate, biotinylated Ras peptide, 50 mM HEPES, pH 7.5, a

10 modulating anion (for example 10 mM glycerophosphate or 5mM ATP), 5 mM MgCl$_2$, 10 μM ZnCl$_2$, 0.1% PEG (15,000-20,000 mw), 2 mM dithiothreitol, and geranylgeranyl-protein transferase type I(GGTase). The GGTase-type I enzyme employed in the assay is prepared as described in U.S. Pat. No. 5,470,832, incorporated by

15 reference. The Ras peptide is derived from the K4B-Ras protein and has the following sequence: biotinyl-GKKKKKKSKTKCVIM (single amino acid code) (SEQ.ID.NO.: 2). Reactions are initiated by the addition of GGTase and stopped at timed intervals (typically 15 min) by the addition of 200 μL of a 3 mg/mL

20 suspension of streptavidin SPA beads (Scintillation Proximity Assay beads, Amersham) in 0.2 M sodium phosphate, pH 4, containing 50 mM EDTA, and 0.5% BSA. The quenched reactions are allowed to stand for 2 hours before analysis on a Packard TopCount scintillation counter.

25   For inhibition studies, assays are run as described above, except inhibitors are prepared as concentrated solutions in 100% dimethyl sulfoxide and then diluted 25-fold into the enzyme assay mixture. IC$_{50}$ values are determined with Ras peptide near K$_M$ concentrations. Enzyme and substrate

30 concentrations for inhibitor IC$_{50}$ determinations are as follows: 75 pM GGTase-I, 1.6 μM Ras peptide, 100 nM geranylgeranyl diphosphate.

        The compounds of the instant invention described in the above Examples 3-15 were tested for inhibitory activity

against human GGTase type I by the assay described above and were found to have IC$_{50}$ of ≤ 5 µM.

EXAMPLE 18

Cell-based in vitro ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. et al., Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labeled in 3 ml methionine-free DMEM supple-mented with 10% regular DMEM, 2% fetal bovine serum and 400 µCi[^{35}S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl$_2$/1mM DTT/10 mg/ml aprotinen/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are bought to 1 ml with IP buffer (lysis buffer lacking DTT) and immuno-precipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 µl of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immuno-precipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins

are compared to determine the percent inhibition of farnesyl transfer to protein.

EXAMPLE 19

Cell-basedin vitro growth inhibition assay

To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a v-ras, v-raf, or v-mos oncogene is tested. Cells transformed by v-Raf and v-Mos maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either v-ras, v-raf, or v-mos are seeded at a density of 1×10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

EXAMPLE 20

Construction of SEAP reporter plasmid pDSE100

The SEAP reporter plasmid, pDSE100 was constructed by ligating a restriction fragment containing the SEAP coding sequence into the plasmid pCMV-RE-AKI. The SEAP gene is

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derived from the plasmid pSEAP2-Basic (Clontech, Palo Alto, CA).
The plasmid pCMV-RE-AKI was constructed by Deborah Jones
(Merck) and contains 5 sequential copies of the 'dyad symmetry
response element' cloned upstream of a 'CAT-TATA' sequence

5   derived from the cytomegalovirus immediate early promoter. The
plasmid also contains a bovine growth hormone poly-A sequence.
        The plasmid, pDSE100 was constructed as follows. A
restriction fragment encoding the SEAP coding sequence was cut
out of the plasmid pSEAP2-Basic using the restriction enzymes

10   EcoR1 and HpaI. The ends of the linear DNA fragments were
filled in with the Klenow fragment of E. coli DNA Polymerase I.
The 'blunt ended' DNA containing the SEAP gene was isolated by
electrophoresing the digest in an agarose gel and cutting out the
1694 base pair fragment. The vector plasmid pCMV-RE-AKI was

15   linearized with the restriction enzyme Bgl-II and the ends filled in
with Klenow DNA Polymerase I. The SEAP DNA fragment was
blunt end ligated into the pCMV-RE-AKI vector and the ligation
products were transformed into DH5-alpha E. coli cells (Gibco-
BRL). Transformants were screened for the proper insert and

20   then mapped for restriction fragment orientation. Properly
oriented recombinant constructs were sequenced across the
cloning junctions to verify the correct sequence.   The resulting
plasmid contains the SEAP coding sequence downstream of the
DSE and CAT-TATA promoter elements and upstream of the BGH

25   poly-A sequence.

Alternative Construction of SEAP reporter plasmid, pDSE101
        The SEAP repotrer plasmid, pDSE101 is also
constructed by ligating a restriction fragment containing the

30   SEAP coding sequence into the plasmid pCMV-RE-AKI. The SEAP
gene is derived from plasmid pGEM7zf(-)/SEAP.
        The plasmid pDSE101 was constructed as follows: A
restriction fragment containing part of the SEAP gene coding
sequence was cut out of the plasmid pGEM7zf(-)/SEAP using the

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restriction enzymes Apa I and KpnI. The ends of the linear DNA
fragments were chewed back with the Klenow fragment of E. coli
DNA Polymerase I. The "blunt ended" DNA containing the
truncated SEAP gene was isolated by electrophoresing the digest

5   in an agarose gel and cutting out the 1910 base pair fragment.
This 1910 base pair fragment was ligated into the plasmid pCMV-
RE-AKI which had been cut with Bgl-II and filled in with E. coli
Klenow fragment DNA polymerase. Recombinant plasmids were
screened for insert orientation and sequenced through the ligated

10   junctions. The plasmid pCMV-RE-AKI is derived from plasmid
pCMVIE-AKI-DHFR (Whang , Y., Silberklang, M., Morgan, A.,
Munshi, S., Lenny, A.B., Ellis, R.W., and Kieff, E. (1987) J. Virol., 61,
1796-1807) by removing an EcoRI fragment containing the DHFR
and Neomycin markers. Five copies of the fos promoter serum

15   response element were inserted as described previously (Jones,
R.E., Defeo-Jones, D., McAvoy, E.M., Vuocolo, G.A., Wegrzyn, R.J.,
Haskell, K.M. and Oliff, A. (1991) Oncogene, 6, 745-751) to create
plasmid pCMV-RE-AKI.

           The plasmid pGEM7zf(-)/SEAP was constructed as

20   follows. The SEAP gene was PCRed, in two segments from a
human placenta cDNA library (Clontech) using the following
oligos.

Sense strand N-terminal SEAP : 5'
25   GAGAGGGAATTCGGGCCCTTCCTGCAT
GCTGCTGCTGCTGCTGCTGGGC 3' (SEQ.ID.NO.:3)

Antisense strand N-terminal SEAP: 5'
GAGAGAGCTCGAGGTTAACCCGGGT
30   GCGCGGCGTCGGTGGT 3' (SEQ.ID.NO.:4)

Sense strand C-terminal SEAP: 5'
GAGAGAGTCTAGAGTTAACCCGTGGTCC
CCGCGTTGCTTCCT 3' (SEQ.ID.NO.:5)

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Antisense strand C-terminal SEAP: 5'
GAAGAGGAAGCTTGGTACCGCCACTG
GGCTGTAGGTGGTGGCT 3' (SEQ.ID.NO.:6)

5

The N-terminal oligos (SEQ.ID.NO.: 4 and SEQ.ID.NO.: 5) were
used to generate a 1560 bp N-terminal PCR product that
contained EcoRI and HpaI restriction sites at the ends. The
Antisense N-terminal oligo (SEQ.ID.NO.: 4) introduces an internal
10   translation STOP codon within the SEAP gene along with the
HpaI site. The C-terminal oligos (SEQ.ID.NO.: 5 and SEQ.ID.NO.:
6) were used to amplify a 412 bp C-terminal PCR product
containing HpaI and HindIII restriction sites. The sense strand
C-terminal oligo (SEQ.ID.NO.: 5) introduces the internal STOP
15   codon as well as the HpaI site. Next, the N-terminal amplicon was
digested with EcoRI and HpaI while the C-terminal amplicon was
digested with HpaI and HindIII. The two fragments comprising
each end of the SEAP gene were isolated by electrophoresing the
digest in an agarose gel and isolating the 1560 and 412 base pair
20   fragments. These two fragments were then co-ligated into the
vector pGEM7zf(-) (Promega) which had been restriction digested
with EcoRI and HindIII and isolated on an agarose gel. The
resulting clone, pGEM7zf(-)/SEAP contains the coding sequence
for the SEAP gene from amino acids.

25

<u>Construction of a constitutively expressing SEAP plasmid pCMV-
SEAP</u>

An expression plasmid constitutively expressing the
SEAP protein was created by placing the sequence encoding a
30   truncated SEAP gene downstream of the cytomegalovirus (CMV)
IE-1 promoter. The expression plasmid also includes the CMV
intron A region 5' to the SEAP gene as well as the 3' untranslated
region of the bovine growth hormone gene 3' to the SEAP gene.

The plasmid pCMVIE-AKI-DHFR (Whang et al, 1987)
containing the CMV immediate early promoter was cut with
EcoRI generating two fragments. The vector fragment was
isolated by agarose electrophoresis and religated. The resulting

5   plasmid is named pCMV-AKI. Next, the cytomegalovirus intron A
nucleotide sequence was inserted downstream of the CMV IE1
promter in pCMV-AKI. The intron A sequence was isolated from a
genomic clone bank and subcloned into pBR322 to generate
plasmid p16T-286. The intron A sequence was mutated at

10   nucleotide 1856 (nucleotide numbering as in Chapman, B.S.,
Thayer, R.M., Vincent, K.A. and Haigwood, N.L., Nuc.Acids Res. 19,
3979-3986) to remove a SacI restriction site using site directed
mutagenesis. The mutated intron A sequence was PCRed from
the plasmid p16T-287 using the following oligos.

15

Sense strand: 5' GGCAGAGCTCGTTTAGTGAACCGTCAG 3'
(SEQ.ID.NO.: 7)

Antisense strand: 5' GAGAGATCTCAAGGACGGTGACTGCAG 3'
20   (SEQ.ID.NO.: 8)

These two oligos generate a 991 base pair fragment
with a SacI site incorporated by the sense oligo and a Bgl-II
fragment incorporated by the antisense oligo. The PCR fragment

25   is trimmed with SacI and Bgl-II and isolated on an agarose gel.
The vector pCMV-AKI is cut with SacI and Bgl-II and the larger
vector fragment isolated by agarose gel electrophoresis. The two
gel isolated fragments are ligated at their respective SacI and Bgl-
II sites to create plasmid pCMV-AKI-InA.

30   The DNA sequence encoding the truncated SEAP gene
is inserted into the pCMV-AKI-InA plasmid at the Bgl-II site of the
vector. The SEAP gene is cut out of plasmid pGEM7zf(-)/SEAP
(described above) using EcoRI and HindIII. The fragment is filled
in with Klenow DNA polymerase and the 1970 base pair fragment

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isolated from the vector fragment by agarose gel electrophoresis. The pCMV-AKI-InA vector is prepared by digesting with Bgl-II and filling in the ends with Klenow DNA polymerase. The final construct is generated by blunt end ligating the SEAP fragment

5   into the pCMV-AKI-InA vector. Transformants were screened for the proper insert and then mapped for restriction fragment orientation. Properly oriented recombinant constructs were sequenced across the cloning junctions to verify the correct sequence. The resulting plasmid, named pCMV-SEAP, contains a

10   modified SEAP sequence downstream of the cytomegalovirus immediately early promoter IE-1 and intron A sequence and upstream of the bovine growth hormone poly-A sequence. The plasmid expresses SEAP in a constitutive manner when transfected into mammalian cells.

15

Cloning of a Myristylated viral-H-ras expression plasmid
         A DNA fragment containing viral-H-ras can be PCRed from plasmid "H-1" (Ellis R. et al. J. Virol. 36, 408, 1980) or "HB-11 (deposited in the ATCC under Budapest Treaty on August 27,

20   1997, and designated ATCC 209,218) using the following oligos.

Sense strand:
5'TCTCCTCGAGGCCACCATGGGGAGTAGCAAGAGCAAGCCTAAG
GACCCCAGCCAGCGCCGGATGACAGAATACAAGCTTGTGGTGG

25   3'. (SEQ.ID.NO.: 9)

Antisense:
5'CACATCTAGATCAGGACAGCACAGACTTGCAGC 3'.
(SEQ.ID.NO.: 10)

30

         A sequence encoding the first 15 aminoacids of the v-src gene, containing a myristylation site, is incorporated into the sense strand oligo. The sense strand oligo also optimizes the 'Kozak' translation initiation sequence immediately 5' to the ATG

35   start site. To prevent prenylation at the viral-ras C-terminus,

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cysteine 186 would be mutated to a serine by substituting a G residue for a C residue in the C-terminal antisense oligo. The PCR primer oligos introduce an XhoI site at the 5' end and a XbaI site at the 3'end. The XhoI-XbaI fragment can be ligated into the

5   mammalian expression plasmid pCI (Promega) cut with XhoI and XbaI. This results in a plasmid in which the recombinant myr-viral-H-ras gene is constitutively transcribed from the CMV promoter of the pCI vector.

10   <u>Cloning of a viral-H-ras-CVLL expression plasmid</u>

A viral-H-ras clone with a C-terminal sequence encoding the amino acids CVLL can be cloned from the plasmid "H-1" (Ellis R. et al. J. Virol. 36, 408, 1980) or "HB-11 (deposited in the ATCC under Budapest Treaty on August 27, 1997, and

15   designated ATCC 209,218) by PCR using the following oligos.

<u>Sense strand:</u>
5'TCTCCTCGAGGCCACCATGACAGAATACAAGCTTGTGGTGG-3'
(SEQ.ID.NO.: 11)

20

<u>Antisense strand:</u>
5'CACTCTAGACTGGTGTCAGAGCAGCACACACTTGCAGC-3'
(SEQ.ID.NO.: 12)

25   The sense strand oligo optimizes the 'Kozak' sequence and adds an XhoI site. The antisense strand mutates serine 189 to leucine and adds an XbaI site. The PCR fragment can be trimmed with XhoI and XbaI and ligated into the XhoI-XbaI cut vector pCI (Promega). This results in a plasmid in which the mutated viral-

30   H-ras-CVLL gene is constitutively transcribed from the CMV promoter of the pCI vector.

<u>Cloning of c-H-ras-Leu61 expression plasmid</u>

The human c-H-ras gene can be PCRed from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

5

<u>Sense strand:</u>
5'-GAGAGAATTCGCCACCATGACGGAATATAAGCTGGTGG-3'
(SEQ.ID.NO.: 13)

10   <u>Antisense strand:</u>
5'-GAGAGTCGACGCGTCAGGAGAGCACACACTTGC-3'
(SEQ.ID.NO.: 14)

The primers will amplify a c-H-ras encoding DNA
15   fragment with the primers contributing an optimized 'Kozak' translation start sequence, an EcoRI site at the N-terminus and a Sal I stite at the C-terminal end. After trimming the ends of the PCR product with EcoRI and Sal I, the c-H-ras fragment can be ligated ligated into an EcoRI -Sal I cut mutagenesis vector pAlter-
20   1 (Promega). Mutation of glutamine-61 to a leucine can be accomplished using the manufacturer's protocols and the following oligonucleotide:

5'-CCGCCGGCCTGGAGGAGTACAG-3' (SEQ.ID.NO.: 15)
25

After selection and sequencing for the correct nucleotide substitution, the mutated c-H-ras-Leu61 can be excised from the pAlter-1 vector, using EcoRI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested
30   with EcoRI and Sal I. The new recombinant plasmid will constitutively transcribe c-H-ras-Leu61 from the CMV promoter of the pCI vector.

Cloning of a c-N-ras-Val-12 expression plasmid

The human c-N-ras gene can be PCRed from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

5

Sense strand:
5'-GAGAGAATTCGCCACCATGACTGAGTACAAACTGGTGG-3' (SEQ.ID.NO.: 16)

10   Antisense strand:
5'-GAGAGTCGACTTGTTACATCACCACACATGGC-3' (SEQ.ID.NO.: 17)

The primers will amplify a c-N-ras encoding DNA
15   fragment with the primers contributing an optimized 'Kozak' translation start sequence, an EcoRI site at the N-terminus and a Sal I stite at the C-terminal end. After trimming the ends of the PCR product with EcoRI and Sal I, the c-N-ras fragment can be ligated into an EcoRI -Sal I cut mutagenesis vector pAlter-1
20   (Promega). Mutation of glycine-12 to a valine can be accomplished using the manufacturer's protocols and the following oligonucleotide:

5'-GTTGGAGCAGTTGGTGTTGGG-3' (SEQ.ID.NO.: 18)
25

After selection and sequencing for the correct nucleotide substitution, the mutated c-N-ras-Val-12 can be excised from the pAlter-1 vector, using EcoRI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested
30   with EcoRI and Sal I. The new recombinant plasmid will constitutively transcribe c-N-ras-Val-12 from the CMV promoter of the pCI vector.

Cloning of a c-K-ras-Val-12 expression plasmid

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The human c-K-ras gene can be PCRed from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

5 <u>Sense strand:</u>
5'-GAGAGGTACCGCCACCATGACTGAATATAAACTTGTGG-3' (SEQ.ID.NO.: 19)

<u>Antisense strand:</u>
10 5'-CTCTGTCGACGTATTTACATAATTACACACTTTGTC-3' (SEQ.ID.NO.: 20)

The primers will amplify a c-K-ras encoding DNA fragment with the primers contributing an optimized 'Kozak'
15 translation start sequence, a KpnI site at the N-terminus and a Sal I stite at the C-terminal end. After trimming the ends of the PCR product with Kpn I and Sal I, the c-K-ras fragment can be ligated into a KpnI -Sal I cut mutagenesis vector pAlter-1 (Promega). Mutation of cysteine-12 to a valine can be accomplished using the
20 manufacturer's protocols and the following oligonucleotide:

5'-GTAGTTGGAGCTGTTGGCGTAGGC-3' (SEQ.ID.NO.: 21)

After selection and sequencing for the correct
25 nucleotide substitution, the mutated c-K-ras-Val-12 can be excised from the pAlter-1 vector, using KpnI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested with KpnI and Sal I. The new recombinant plasmid will constitutively transcribe c-K-ras-Val-12 from the CMV promoter of
30 the pCI vector.

<u>SEAP assay</u>
Human C33A cells (human epitheial carcenoma - ATTC collection) are seeded in 10cm tissue culture plates in DMEM +
35 10% fetal calf serum + 1X Pen/Strep + 1X glutamine + 1X NEAA.

Cells are grown at 37°C in a 5% CO_2 atmosphere until they reach 50 -80% of confluency.

The transient transfection is performed by the $CaPO_4$ method (Sambrook et al., 1989). Thus, expression plasmids for H-ras, N-ras, K-ras, Myr-ras or H-ras-CVLL are co-precipitated with the DSE-SEAP reporter construct. For 10cm plates 600μl of $CaCl_2$ -DNA solution is added dropwise while vortexing to 600μl of 2X HBS buffer to give 1.2ml of precipitate solution (see recipes below). This is allowed to sit at room temperature for 20 to 30 minutes. While the precipitate is forming, the media on the C33A cells is replaced with DMEM (minus phenol red; Gibco cat. # 31053-028)+ 0.5% charcoal stripped calf serum + 1X (Pen/Strep, Glutamine and nonessential aminoacids). The $CaPO_4$-DNA precipitate is added dropwise to the cells and the plate rocked gently to distribute. DNA uptake is allowed to proceed for 5-6 hrs at 37°C under a 5% CO_2 atmosphere.

Following the DNA incubation period, the cells are washed with PBS and trypsinized with 1ml of 0.05% trypsin. The 1 ml of trypsinized cells is diluted into 10ml of phenol red free DMEM + 0.2% charcoal stripped calf serum + 1X (Pen/Strep, Glutamine and NEAA). Transfected cells are plated in a 96 well microtiter plate (100μl/well) to which drug, diluted in media, has already been added in a volume of 100μl. The final volume per well is 200μl with each drug concentration repeated in triplicate over a range of half-log steps.

Incubation of cells and drugs is for 36 hrs at 37°C under CO_2. At the end of the incubation period, cells are examined microscopically for evidence of cell distress. Next, 100μl of media containing the secreted alkaline phosphatase is removed from each well and transferred to a microtube array for heat treatment at 65°C for 1 hr to inactivate endogenous alkaline phosphatases (but not the heat stable secreted phosphatase).

The heat treated media is assayed for alkaline phosphatase by a luminescence assay using the luminescence

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reagent CSPD® (Tropix, Bedford, Mass.). A volume of 50 μl media is combined with 200 μl of CSPD cocktail and incubated for 60 minutes at room temperature. Luminesence is monitored using an ML2200 microplate luminometer (Dynatech). Luminescence

5   reflects the level of activation of the fos reporter construct stimulated by the transiently expressed protein.

DNA-CaPO4 precipitate for 10cm. plate of cells

Ras expression plasmid (1μg/μl)	10μl
DSE-SEAP Plasmid (1μg/μl)	2μl
Sheared Calf Thymus DNA (1μg/μl)	8μl
2M CaCl$_2$	74μl
dH$_2$O	506μl

15   ### 2X HBS Buffer

280mM NaCl

10mM KCl

1.5mM Na$_2$HPO$_4$ 2H$_2$O

12mM dextrose

20   50mM HEPES

Final pH = 7.05

Luminesence Buffer (26ml)

Assay Buffer	20ml
Emerald Reagent™ (Tropix)	2.5ml
100mM homoarginine	2.5ml
CSPD Reagent® (Tropix)	1.0ml

Assay Buffer

Add 0.05M Na$_2$CO$_3$ to 0.05M NaHCO$_3$ to obtain pH 9.5.

Make 1mM in MgCl$_2$

30

EXAMPLE 21

The processing assays employed are modifications of that described by DeClue et al [Cancer Research 51, 712-717, 1991].

35

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K4B-Ras processing inhibition assay

PSN-1 (human pancreatic carcinoma) or viral-K4B-ras-transformed Rat1 cells are used for analysis of protein processing. Subconfluent cells in 100 mm dishes are fed with 3.5 ml of media
5 (methionine-free RPMI supplemented with 2% fetal bovine serum or cysteine-free/methionine-free DMEM supplemented with 0.035 ml of 200 mM glutamine (Gibco), 2% fetal bovine serum, respectively) containing the desired concentration of test compound, lovastatin or solvent alone. Cells treated with
10 lovastatin (5-10 μM), a compound that blocks Ras processing in cells by inhibiting a rate-limiting step in the isoprenoid biosynthetic pathway, serve as a positive control. Test compounds are prepared as 1000x concentrated solutions in DMSO to yield a final solvent concentration of 0.1%. Following
15 incubation at 37ºC for two hours 204 μCi/ml [^{35}S]Pro-Mix (Amersham, cell labeling grade) is added.

After introducing the label amino acid mixture, the cells are incubated at 37°C for an additional period of time (typically 6 to 24 hours). The media is then removed and the cells
20 are washed once with cold PBS. The cells are scraped into 1 ml of cold PBS, collected by centrifugation (10,000 x g for 10 sec at room temperature), and lysed by vortexing in 1 ml of lysis buffer (1% Nonidet P-40, 20 mM HEPES, pH 7.5, 150 mM NaCl, 1 mM EDTA, 0.5% deoxycholate, 0.1% SDS, 1 mM DTT, 10 μg/ml AEBSF, 10 μg/ml
25 aprotinin, 2 μg/ml leupeptin and 2 μg/ml antipain). The lysate is then centrifuged at 15,000 x g for 10 min at 4°C and the supernatant saved.

For immunoprecipitation of Ki4B-Ras, samples of lysate supernatant containing equal amounts of protein are
30 utilized. Protein concentration is determined by the bradford method utilizing bovine serum albumin as a standard. The appropriate volume of lysate is brought to 1 ml with lysis buffer lacking DTT and 8 μg of the pan Ras monoclonal antibody, Y13-259, added. The protein/antibody mixture is incubated on ice at

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4°C for 24 hours. The immune complex is collected on pansorbin (Calbiochem) coated with rabbit antiserum to rat IgG (Cappel) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and

5   resuspended in 100 μl elution buffer (10 mM Tris pH 7.4, 1% SDS). The Ras is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation (15,000 x g for 30 sec. at room temperature).

The supernatant is added to 1 ml of Dilution Buffer

10   0.1% Triton X-100, 5 mM EDTA, 50 mM NaCl, 10 mM Tris pH 7.4) with 2 μg Kirsten-ras specific monoclonal antibody, c-K-ras Ab-1 (Calbiochem). The second protein/antibody mixture is incubated on ice at 4°C for 1-2 hours. The immune complex is collected on pansorbin (Calbiochem) coated with rabbit antiserum to rat IgG

15   (Cappel) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in Laemmli sample buffer. The Ras is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation. The

20   supernatant is subjected to SDS-PAGE on a 12% acrylamide gel (bis-acrylamide:acrylamide, 1:100), and the Ras visualized by fluorography.

hDJ processing inhibition assay

25   PSN-1 cells are seeded in 24-well assay plates. For each compound to be tested, the cells are treated with a minimum of seven concentrations in half-log steps. The final solvent (DMSO) concentration is 0.1%. A vehicle-only control is included on each assay plate. The cells are treated for 24 hours at 37°C / 5%

30   CO_2.

The growth media is then aspirated and the samples are washed with PBS. The cells are lysed with SDS-PAGE sample buffer containing 5% 2-mercaptoethanol and heated to 95°C for 5

minutes. After cooling on ice for 10 minutes, a mixture of nucleases is added to reduce viscosity of the samples.

The plates are incubated on ice for another 10 minutes. The samples are loaded onto pre-cast 8% acrylamide gels and electrophoresed at 15 mA/gel for 3-4 hours. The samples are then transferred from the gels to PVDF membranes by Western blotting.

The membranes are blocked for at least 1 hour in buffer containing 2% nonfat dry milk. The membranes are then treated with a monoclonal antibody to hDJ-2 (Neomarkers Cat. # MS-225), washed, and treated with an alkaline phosphatase-conjugated secondary antibody. The membranes are then treated with a fluorescent detection reagent and scanned on a phosphorimager.

For each sample, the percent of total signal corresponding to the unprenylated species of hDJ (the slower-migrating species) is calculated by densitometry. Dose-response curves and EC_{50} values are generated using 4-parameter curve fits in SigmaPlot software.

EXAMPLE 22

Rap1 processing inhibition assay

Protocol A:

Cells are labeled, incubated and lysed as described in Example 21.

For immunoprecipitation of Rap1, samples of lysate supernatant containing equal amounts of protein are utilized. Protein concentration is determined by the bradford method utilizing bovine serum albumin as a standard. The appropriate volume of lysate is brought to 1 ml with lysis buffer lacking DTT and 2 μg of the Rap1 antibody, Rap1/Krev1 (121) (Santa Cruz Biotech), is added. The protein/antibody mixture is incubated on

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The compounds to be assayed are diluted in DMSO in 1/2-log dilutions. The range of final concentrations to be assayed is generally 0.1-100μM. Four concentrations per compound is typical. The compounds are diluted so that each concentration is

5   1000x of the final concentration (i.e., for a 10μM data point, a 10mM stock of the compound is needed).

2μL of each 1000x compound stock is diluted into 1ml media to produce a 2X stock of compound. A vehicle control solution (2μL DMSO to 1ml media), is utilized. 0.5 ml of the 2X

10   stocks of compound are added to the cells.

After 24 hours, the media is aspirated from the assay plates. Each well is rinsed with 1ml PBS, and the PBS is aspirated. 180μL SDS-PAGE sample buffer (Novex) containing 5% 2-mercapto-ethanol-is-added to each well. The plates are heated

15   to 100°C for 5 minutes using a heat block containing an adapter for assay plates. The plates are placed on ice. After 10 minutes, 20μL of an RNAse/DNase mix is added per well. This mix is 1mg/ml DNaseI (Worthington Enzymes), 0.25mg/ml Rnase A (Worthington Enzymes), 0.5M Tris-HCl pH8.0 and 50mM $MgCl_2$.

20   The plate is left on ice for 10 minutes. Samples are then either loaded on the gel, or stored at -70°C until use.

Each assay plate (usually 3 compounds, each in 4-point titrations, plus controls) requires one 15-well 14% Novex gel. 25μl of each sample is loaded onto the gel. The gel is run at

25   15mA for about 3.5 hours. It is important to run the gel far enough so that there will be adequate separation between 21kd (Rap1) and 29kd (Rab6).

The gels are then transferred to Novex pre-cut PVDF membranes for 1.5 hours at 30V (constant voltage).

30   Immediately after transferring, the membranes are blocked overnight in 20ml Western blocking buffer (2% nonfat dry milk in Western wash buffer (PBS + 0.1% Tween-20). If blocked over the weekend, 0.02% sodium azide is added. The membranes are blocked at 4°C with slow rocking.

ice at 4°C for 1 hour. The immune complex is collected on pansorbin (Calbiochem) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in 100 μl elution buffer (10

5   mM Tris pH 7.4, 1% SDS). The Rap1 is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation (15,000 x g for 30 sec. at room temperature).

The supernatant is added to 1 ml of Dilution Buffer

10   (0.1% Triton X-100, 5 mM EDTA, 50 mM NaCl, 10 mM Tris pH 7.4) with 2 μg Rap1 antibody, Rap1/Krev1 (121) (Santa Cruz Biotech). The second protein/antibody mixture is incubated on ice at 4°C for 1-2 hours. The immune complex is collected on pansorbin (Calbiochem) by tumbling at 4°C for 45 minutes. The pellet is

15   washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in Laemmli sample buffer. The Rap1 is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation. The supernatant is subjected to SDS-PAGE on a 12% acrylamide gel

20   (bis-acrylamide:acrylamide, 1:100), and the Rap1 visualized by fluorography.

Protocol B:

PSN-1 cells are passaged every 3-4 days in 10cm plates,

25   splitting near-confluent plates 1:20 and 1:40. The day before the assay is set up, 5×10^6 cells are plated on 15cm plates to ensure the same stage of confluency in each assay. The media for these cells is RPM1 1640 (Gibco), with 15% fetal bovine serum and 1x Pen/Strep antibiotic mix.

30   The day of the assay, cells are collected from the 15cm plates by trypsinization and diluted to 400,000 cells/ml in media. 0.5ml of these diluted cells are added to each well of 24-well plates, for a final cell number of 200,000 per well. The cells are then grown at 37C overnight.

The blocking solution is discarded and 20ml fresh blocking solution containing the anti Rap1a antibody (Santa Cruz Biochemical SC1482) at 1:1000 (diluted in Western blocking buffer) and the anti Rab6 antibody (Santa Cruz Biochemical

5   SC310) at 1:5000 (diluted in Western blocking buffer) are added. The membranes are incubated at room temperature for 1 hour with mild rocking. The blocking solution is then discarded and the membrane is washed 3 times with Western wash buffer for 15 minutes per wash. 20ml blocking solution containing 1:1000

10   (diluted in Western blocking buffer) each of two alkaline phosphatase conjugated antibodies (Alkaline phosphatase conjugated Anti-goat IgG and Alkaline phosphatase conjugated anti-rabbit IgG [Santa Cruz Biochemical]) is then added. The membrane is incubated for one hour and washed 3x as above.

15   About 2ml per gel of the Amersham ECF detection reagent is placed on an overhead transparency (ECF) and the PVDF membranes are placed face-down onto the detection reagent. This is incubated for one minute, then the membrane is placed onto a fresh transparency sheet.

20   The developed transparency sheet is scanned on a phosphorimager and the Rap1a Minimum Inhibitory Concentration is determined from the lowest concentration of compound that produces a detectable Rap1a Western signal. The Rap1a antibody used recognizes only unprenylated/unprocessed

25   Rap1a, so that the precence of a detectable Rap1a Western signal is indicative of inhibition of Rap1a prenylation.

Protocol C

This protocol allows the determination of an EC_{50} for

30   inhibition of processing of Rap1a. The assay is run as described in Protocol B with the following modifications. 20 μl of sample is run on pre-cast 10-20% gradient acrylamide mini gels (Novex Inc.) at 15 mA/gel for 2.5-3 hours. Prenylated and unprenylated forms of Rap1a are detected by blotting with a polyclonal antibody

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(Rap1/Krev-1 Ab#121; Santa Cruz Research Products #sc-65), followed by an alkaline phosphatase-conjugated anti-rabbit IgG antibody. The percentage of unprenylated Rap1a relative to the total amount of Rap1a is determined by peak integration using

5   Imagequant6 software (Molecular Dynamics). Unprenylated Rap1a is distinguished from prenylated protein by virtue of the greater apparent molecular weight of the prenylated protein. Dose-response curves and EC_{50} values are generated using 4-parameter curve fits in SigmaPlot software.

10

EXAMPLE 23

In vivo tumor growth inhibition assay (nude mouse)

In vivo efficacy as an inhibitor of the growth of cancer
15   cells may be confirmed by several protocols well known in the art. Examples of such in vivo efficacy studies are described by N. E. Kohl et al. (Nature Medicine, 1:792-797 (1995)) and N. E. Kohl et al. (Proc. Nat. Acad. Sci. U.S.A., 91:9141-9145 (1994)).

Rodent fibroblasts transformed with oncogenically
20   mutated human Ha-ras or Ki-ras (10^6 cells/animal in 1 ml of DMEM salts) are injected subcutaneously into the left flank of 8-12 week old female nude mice (Harlan) on day 0. The mice in each oncogene group are randomly assigned to a vehicle, compound or combination treatment group. Animals are dosed subcutaneously
25   starting on day 1 and daily for the duration of the experiment. Alternatively, the farnesyl-protein transferase inhibitor may be administered by a continuous infusion pump. Compound, compound combination or vehicle is delivered in a total volume of 0.1 ml. Tumors are excised and weighed when all of the vehicle-
30   treated animals exhibited lesions of 0.5 - 1.0 cm in diameter, typically 11-15 days after the cells were injected. The average weight of the tumors in each treatment group for each cell line is calculated.

WHAT IS CLAIMED IS:

1.   A compound which is:

A

wherein:

R^{1a} and R^{1b} are independently selected from:

    a)   hydrogen,

    b)   aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

    c)   unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{1c} is independently selected from:

    a)   hydrogen,

    b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl,

C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,

    c)   unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$ and $R^{11}OC(O)$-NR^{10}-;or two R^{1c}s on the same carbon are combined with that carbon to form a C_4-C_6 cycloalkyl;

R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,

wherein the substituted group is substituted with one or more of:

20   1) aryl or heterocycle, unsubstituted or substituted with:

        a) C_{1-4} alkyl,

        b) $(CH_2)_pOR^6$,

        c) $(CH_2)_pNR^6R^7$,

        d) halogen,

        e) CN,

        f) aryl or heteroaryl,

        g) perfluoro-C_{1-4} alkyl,

        h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},

    2) C_{3-6} cycloalkyl,

    3) OR^6,

    4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},

5) $-NR^6R^7$

6) R^6
        $-N-C-R^7$
              $\parallel$
              O

7) R^6
        $-N-C-NR^7R^{7a}$
              $\parallel$
              O

8) $-O-C-NR^6R^7$
              $\parallel$
              O

9) $-O-C-OR^6$
              $\parallel$
              O

10) $C-NR^6R^7$
        $\parallel$
        O

11) $-SO_2-NR^6R^7$

12) R^6
        $-N-SO_2-R^{6a}$

13) $C-R^6$
        $\parallel$
        O

14) $C-OR^6$
        $\parallel$
        O

15) N_3,

16)   F,   or

17)   perfluoro-C_{1-4}-alkyl; or

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R^2 and R^3 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, $-NC(O)-$, and

5      $-N(COR^{10})-$;

R^4 is selected from H and CH_3;and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

10   R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) aryl or heterocycle,
15   c) halogen,
   d) HO,
   e)
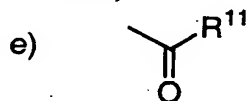
   f) $-SO_2R^{11}$, or
   g) $N(R^{10})_2$; or

20   R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl,
25   unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) aryl or heterocycle,
   c) halogen,
   d) HO,

e)

$$\begin{array}{c} \quad R^{11} \\ \diagup \\ \parallel \\ O \end{array}$$

,

f) $-SO_2R^{11}$,   or

g) $N(R^{10})_2$;

R^8 is independently selected from:

   a)   hydrogen,

   b)   unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO$_2$, $R^{10}C(O)$-, N$_3$, -N(R^{10})$_2$, or $R^{11}OC(O)NR^{10}$-, and

   c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N$_3$, -N(R^{10})$_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

   a)   hydrogen,

   b)   alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO$_2$, $R^{10}C(O)$-, N$_3$, -N(R^{10})$_2$, or $R^{11}OC(O)NR^{10}$-, and

   c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N$_3$, -N(R^{10})$_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)_2N(R^{10})-, -N(R^{10})S(O)_2-, or S(O)_m;

A^3 is selected from: -C(O)-, -C(O)NR^{10}-, -C(O)O-, S(O)_m or a bond;

A^4 is selected from: bond, -O- and -NR^{10}-;

G is H_2 or O, provided that G is not H_2, if A^3 is a bond;

V is selected from:
     a)   hydrogen,
     b)   heterocycle,
     c)   aryl,
     d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
     e) C_2-C_{20} alkenyl, provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

Z is an unsubstituted or substituted multicyclic ring, wherein the substituted multicyclic ring is substituted with one or two moieties selected from the following:
     a) C_{1-4} alkoxy,
     b) NR^6R^7,
     c) C_{3-6} cycloalkyl,

d) -NR^{6}C(O)R^7,

e) HO,

f) -S(O)$_m$R^{6a},

g) halogen,

h) perfluoroalkyl, and

i) C$_{1-4}$ alkyl;

m is	0, 1 or 2;
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
q is	1 or 2;
r is	0 to 5, provided that r is 0 when V is hydrogen;
s is	0 or 1;
t is	0 or 1;
u is	4 or 5; and
v is	0, 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

2.   The compound according to Claim 1 of the formula
B:

wherein:

R^{1a} and R^{1b} are independently selected from:

     a)   hydrogen,

     b)   aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,

     c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^{1c} is independently selected from:

     a)   hydrogen,

     b) $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,

     c)   unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, R^{10}_2N-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ and $R^{11}OC(O)$-NR^{10}-;or two R^{1c}s on the same carbon are combined with that carbon to form a C_4-C_6 cycloalkyl;

R^3 is selected from H and CH_3;

R^2 is selected from H;   [structure: CH₂-C(=O)-NR⁶R⁷]   or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

     1)   aryl,

     2)   heterocycle,

     3) OR^6,

     4) SR^{6a}, SO_2R^{6a}, or

     5)   [structure: CH₂-C(=O)-NR⁶R⁷];

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

     a) C_{1-4} alkoxy,

     b)   halogen, or

c)   aryl or heterocycle;

R^{6a} is selected from: C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b)   halogen, or

c)   aryl or heterocycle;

R^8 is independently selected from:

a)   hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -$N(R^{10})$-, or $S(O)_m$;

A^3 is selected from: -C(O)-, -C(O)NR^{10}-, -C(O)O- or $S(O)_m$;

A^4 is selected from: bond, -O- and -NR^{10}-;

V is selected from:

a)   hydrogen,

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b)   heterocycle selected from pyrrolidinyl, imidazolyl,
         pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl,
         indolyl, quinolinyl, isoquinolinyl, and thienyl,

c)   aryl,

5   d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are
         replaced with a a heteroatom selected from O, S, and
         N, and

e) C_2-C_{20} alkenyl, and provided that V is not hydrogen if
         A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is

10   0 and A^2 is $S(O)_m$;

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring,
wherein the substituted C_7-C_{10} multicyclic alkyl ring is
substituted with one or two moieties selected from the following:

15   a) C_{1-4} alkoxy,

b) NR^6R^7,

c) C_{3-6} cycloalkyl,

d) $-NR^6C(O)R^7$,

e)   HO,

20   f) $-S(O)_mR^{6a}$,

g)   halogen,

h)   perfluoroalkyl, and

i) C_{1-4} alkyl;

25   C_7-C_{10} multicyclic alkyl ring is selected from:

m is	0, 1 or 2;
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
r is	0 to 5, provided that r is 0 when V is hydrogen; and
v is	0, 1, 2 or 3; provided that v is not 0 if A^3 is a bond;

or a pharmaceutically acceptable salt thereof.

3.　　　The compound according to Claim 1 of the formula C:

C

wherein:

R^{1a} and R^{1b} are independently selected from:

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           a)   hydrogen,

           b)   aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,

           c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^{1c} is independently selected from:

           a)   hydrogen,

           b) $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,

           c)   unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ and $R^{11}OC(O)$-NR^{10}-;or two R^{1c}s on the same carbon are combined with that carbon to form a C_4-C_6 cycloalkyl;

R^3 is selected from H and CH_3;

R^2 is selected from H; ![structure showing NR^6R^7 with C=O] or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

           1)   aryl,

           2)   heterocycle,

           3) OR^6,

           4) SR^{6a}, SO_2R^{6a}, or

           5)   ![structure showing NR^6R^7 with C=O];

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b)   halogen, or

c)   aryl or heterocycle;

5   R^{6a} is selected from: C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b)   halogen, or

c)   aryl or heterocycle;

10

R^8 is independently selected from:

a)   hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN,

15   NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

20

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

25

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or $S(O)_m$;

30

A^3 is selected from: -C(O)-, -C(O)NR^{10}-, -C(O)O- or $S(O)_m$;

A^4 is selected from: bond, -O- and -NR^{10}-;

V is selected from:

    a)   hydrogen,

    b)   heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

    c)   aryl,

    d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

    e) C_2-C_{20} alkenyl, and provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring, wherein the substituted C_7-C_{10} multicyclic alkyl ring is substituted with one or two moieties selected from the following:

    a) C_{1-4} alkoxy,

    b) NR^6R^7,

    c) C_{3-6} cycloalkyl,

    d)   -$NR^6C(O)R^7$,

    e)   HO,

    f)   -$S(O)_mR^{6a}$,

    g)   halogen,

    h)   perfluoroalkyl, and

    i) C_{1-4} alkyl;

C_7-C_{10} multicyclic alkyl ring is selected from:

m is   0, 1 or 2;

n is   0, 1, 2, 3 or 4;

p is   0, 1, 2, 3 or 4;

r is   0 to 5, provided that r is 0 when V is hydrogen; and

v is   0, 1, 2 or 3; provided that v is not 0 if A^3 is a bond;

or a pharmaceutically acceptable salt thereof.

4.   The compound according to Claim 2 of the
formula D:

D

wherein:

R^{1a} and R^{1b} are independently selected from:

    a)   hydrogen,

    b)   aryl, heterocycle, cycloalkyl, $R^{10}O\text{-}$, $\text{-N}(R^{10})_2$ or $C_2\text{-}C_6$ alkenyl,

    c) $C_1\text{-}C_6$ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O\text{-}$, or $\text{-N}(R^{10})_2$;

R^{1c} is independently selected from:

    a)   hydrogen,

    b) $R^{10}O\text{-}$, $R^{10}C(O)NR^{10}\text{-}$, $(R^{10})_2NC(O)\text{-}$, $R^{10}{}_2N\text{-}C(NR^{10})\text{-}$, CN, NO_2, $R^{10}C(O)\text{-}$, N_3, $\text{-N}(R^{10})_2$ or $R^{11}OC(O)NR^{10}\text{-}$,

    c)   unsubstituted or substituted $C_1\text{-}C_6$ alkyl wherein the substitutent on the substituted $C_1\text{-}C_6$ alkyl is selected from $R^{10}O\text{-}$, $R^{10}C(O)NR^{10}\text{-}$, $(R^{10})_2NC(O)\text{-}$, $R^{10}{}_2N\text{-}C(NR^{10})\text{-}$, CN, $R^{10}C(O)\text{-}$, N_3, $\text{-N}(R^{10})_2$ and $R^{11}OC(O)\text{-}NR^{10}\text{-}$;

R^3 is selected from H and CH_3;

R^2 is selected from H; [structure: $\overset{NR^6R^7}{\underset{O}{\diagup\!\!\diagdown}}$] ; or $C_{1\text{-}5}$ alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

    1)   aryl,

    2)   heterocycle,

    3) OR^6,

    4) SR^{6a}, SO_2R^{6a}, or

    5)   [structure: $\overset{NR^6R^7}{\underset{O}{\diagup\!\!\diagdown}}$] ;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; $C_{1\text{-}4}$ alkyl, $C_{3\text{-}6}$ cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

    a) $C_{1\text{-}4}$ alkoxy,

    b)   halogen, or

    c)   aryl or heterocycle;

R^{6a} is selected from: C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

   a) C_{1-4} alkoxy,

5   b)   halogen, or

   c)   aryl or heterocycle;

R^8 is independently selected from:

   a)   hydrogen,

10   b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

   c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl,

15         $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

20   R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

25   A^1 is selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or S(O)$_m$;

A^3 is selected from: -C(O)-, -C(O)NR^{10}- or -C(O)O-;

30   A^4 is selected from: bond and -O-;

V is selected from:

   a)   heterocycle selected from pyridinyl and quinolinyl, and

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        b)   aryl;

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring, wherein the substituted C_7-C_{10} multicyclic alkyl ring is

5   substituted with one or two moieties selected from the following:

        a) C_{1-4} alkoxy,

        b) NR^6R^7,

        c) C_{3-6} cycloalkyl,

        d)   -$NR^6C(O)R^7$,

10   e)   HO,

        f)   -$S(O)_mR^{6a}$,

        g)   halogen,

        h)   perfluoroalkyl, and

        i) C_{1-4} alkyl;

15

C_7-C_{10} multicyclic alkyl ring is selected from:
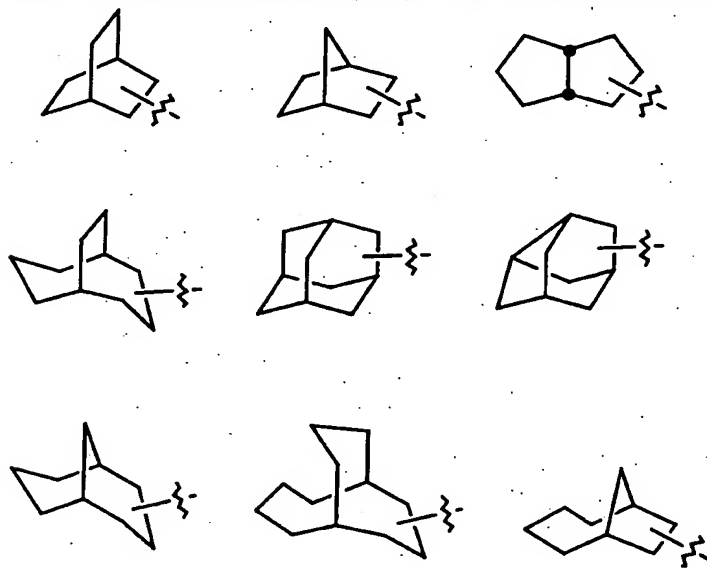
      m is   0, 1 or 2;

20   n is   0, 1, 2, 3 or 4;

      p is   0, 1, 2, 3 or 4;

      r is   0 to 5, and

v is   0, 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

5   5.   The compound according to Claim 3 of the
formula E:

E

wherein:

R^{1a} and R^{1b} are independently selected from:
    a)   hydrogen,
    b)   aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C_2-C_6
        alkenyl,
    c) C_1-C_6 alkyl unsubstituted or substituted by aryl,
        heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, or $-N(R^{10})_2$;

R^{1c} is independently selected from:
    a)   hydrogen,
    b) $R^{10}O-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{10}{}_2N-C(NR^{10})-$,
        CN, NO_2, $R^{10}C(O)-$, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}-$,
    c)   unsubstituted or substituted C_1-C_6 alkyl wherein the
        substitutent on the substituted C_1-C_6 alkyl is selected
        from $R^{10}O-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2NC(O)-$, $R^{10}{}_2N-$
        $C(NR^{10})-$, CN, $R^{10}C(O)-$, N_3, $-N(R^{10})_2$ and $R^{11}OC(O)-$
        $NR^{10}-$;

R^3 is selected from H and CH_3;

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R^2 is selected from H;

$$\underset{O}{\overset{}{\cdot}}\!\!-\!\!C(=O)\!-\!NR^6R^7 ;$$

or $C_{1\text{-}5}$ alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1)   aryl,
2)   heterocycle,
3) OR^6,
4) SR^{6a}, SO_2R^{6a}, or
5) $-C(=O)-NR^6R^7$;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; $C_{1\text{-}4}$ alkyl, $C_{3\text{-}6}$ cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) $C_{1\text{-}4}$ alkoxy,
b)   halogen, or
c)   aryl or heterocycle;

R^{6a} is selected from: $C_{1\text{-}4}$ alkyl or $C_{3\text{-}6}$ cycloalkyl, unsubstituted or substituted with:

a) $C_{1\text{-}4}$ alkoxy,
b)   halogen, or
c)   aryl or heterocycle;

R^8 is independently selected from:

a)   hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O\text{-}$, $R^{10}C(O)NR^{10}\text{-}$, CN, NO_2, $(R^{10})_2N\text{-}C(NR^{10})\text{-}$, $R^{10}C(O)\text{-}$, $\text{-}N(R^{10})_2$, or $R^{11}OC(O)NR^{10}\text{-}$, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O\text{-}$, $R^{10}C(O)NR^{10}\text{-}$, $(R^{10})_2N\text{-}C(NR^{10})\text{-}$, $R^{10}C(O)\text{-}$, $\text{-}N(R^{10})_2$, or $R^{11}OC(O)NR^{10}\text{-}$;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 is selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or S(O)$_m$;

A^3 is selected from: -C(O)-, -C(O)NR^{10}- or -C(O)O-;

A^4 is selected from: bond and -O-;

V is selected from:
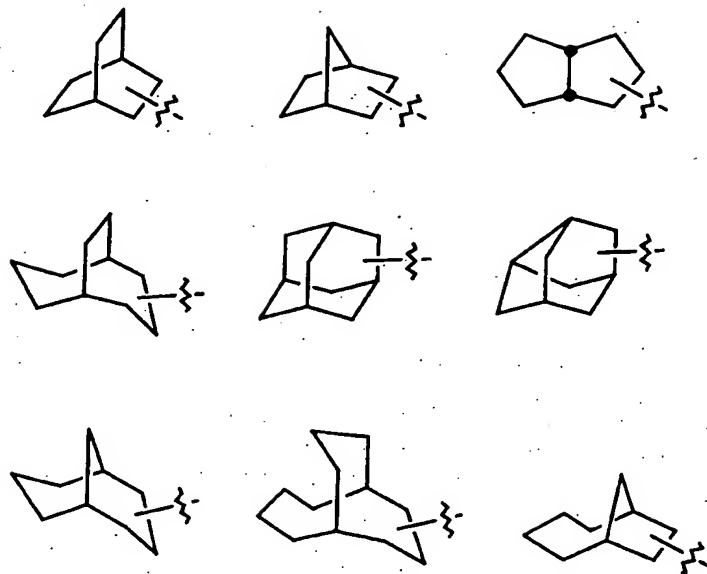 a)   heterocycle selected from pyridinyl and quinolinyl, and
  b)   aryl;

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring, wherein the substituted C_7-C_{10} multicyclic alkyl ring is substituted with one or two moieties selected from the following:
  a) C_{1-4} alkoxy,
  b)   NR^{6}R^7,
  c) C_{3-6} cycloalkyl,
  d)   -NR^{6}C(O)R^7,
  e)   HO,
  f)   -S(O)$_m$R^{6a},
  g)   halogen,
  h)   perfluoroalkyl, and
  i) C_{1-4} alkyl;

C_7-C_{10} multicyclic alkyl ring is selected from:

m is	0, 1 or 2;
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
r is	0 to 5, and
v is	0, 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

6.   The compound according to Claim 4 of the formula F:

$$(R^8)_r \quad R^{9a} \quad \text{...} \quad (CR^{1b}_2)_p \quad \text{—N} \quad R^2 \quad \text{N—A}^3(CR^{1c}_2)_v A^4 Z \quad R^3$$

F

wherein:

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^{1c} is independently selected from:

a) hydrogen,

b) $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ and $R^{11}OC(O)$-NR^{10}-;

R^3 is selected from H and CH_3;

R^2 is selected from H;

$$\begin{array}{c} NR^6R^7 \\ \diagdown\!\!\diagup \\ \| \\ O \end{array}$$
; or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,

2) heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{6a}, or

5)
$$\begin{array}{c} NR^6R^7 \\ \diagdown\!\!\diagup \\ \| \\ O \end{array}$$
;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

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R^{6a} is selected from: C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

    a) C_{1-4} alkoxy,

5   b)   halogen, or

    c)   aryl or heterocycle;

R^8 is independently selected from:

    a)   hydrogen,

10   b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

    c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl,

15            $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

20   R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

25   A^3 is selected from: -C(O)-, -C(O)NR^{10}- or -C(O)O-;

A^4 is selected from: bond and -O-;

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring,
30   wherein the substituted C_7-C_{10} multicyclic alkyl ring is substituted with one or two moieties selected from the following:

    a) C_{1-4} alkoxy,

    b) NR^6R^7,

    c) C_{3-6} cycloalkyl,

d) $-NR^6C(O)R^7$,

e)   HO,

f) $-S(O)_mR^{6a}$,

g)   halogen,

h)   perfluoroalkyl, and

i) C_{1-4} alkyl;

C_7-C_{10} multicyclic alkyl ring is selected from:
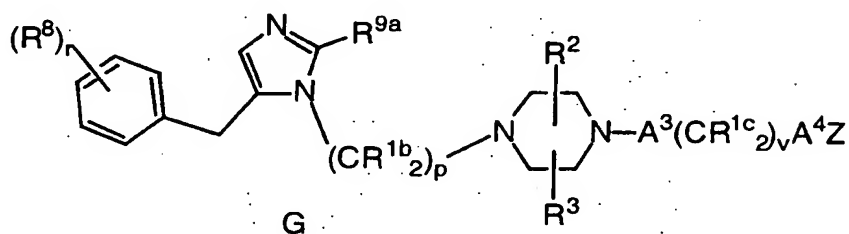

m is   0, 1 or 2;

p is   1, 2 or 3;

r is   0 to 5, and

v is   0, 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

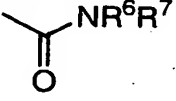7.   The compound according to Claim 5 of the formula G:

G

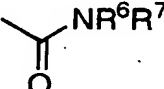wherein:

-166-

R^{1b} is independently selected from:

  a)   hydrogen,

  b)   aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6
       alkenyl,

  c) C_1-C_6 alkyl unsubstituted or substituted by aryl,
       heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^{1c} is independently selected from:

  a)   hydrogen,

  b) $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-,
       CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,

  c)   unsubstituted or substituted C_1-C_6 alkyl wherein the
       substitutent on the substituted C_1-C_6 alkyl is selected
       from $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-
       $C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$ and $R^{11}OC(O)$-
       NR^{10}-;

R^3 is selected from H and CH_3;

R^2 is selected from H; [structure: NR^6R^7 / C=O] or C_{1-5} alkyl, unbranched or
branched, unsubstituted or substituted with one or more of:

  1)   aryl,

  2)   heterocycle,

  3) OR^6,

  4) SR^{6a}, SO_2R^{6a}, or

  5)   [structure: NR^6R^7 / C=O];

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; C_{1-4} alkyl, C_{3-6}
cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

  a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^{6a} is selected from: C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted
5   or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

10   R^8 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6
perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN,
NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or
15   $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl,
$R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-,
-$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

20   R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl
and aryl;

25   R^{11} is independently selected from C_1-C_6 alkyl and aryl;

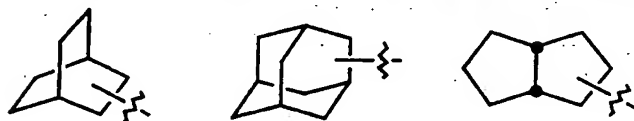A^3 is selected from: -C(O)-, -C(O)NR^{10}- or -C(O)O-;

A^4 is selected from: bond and -O-;
30

Z is an unsubstituted or substituted C_7-C_{10} multicyclic alkyl ring,
wherein the substituted C_7-C_{10} multicyclic alkyl ring is
substituted with one or two moieties selected from the following:

a) C_{1-4} alkoxy,

b)   NR^{6}R^7,

c)   C$_{3-6}$ cycloalkyl,

d)   -NR^{6}C(O)R^7,

e)   HO,

f)   -S(O)$_m$R^{6a},

g)   halogen,

h)   perfluoroalkyl, and

i)   C$_{1-4}$ alkyl;

C$_7$-C$_{10}$ multicyclic alkyl ring is selected from:

m is   0, 1 or 2;

p is   1, 2 or 3;

r is   0 to 5, and

v is   0, 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

8.   A compound which is selected from:

1-(4-Cyanobenzyl)-5-[1-(2-oxo-2-(adamant-1-yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole

R/S 1-(4-Cyanobenzyl)-5-[1-(2-hydroxy-2-(adamant-1-yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole

1-(4-Cyanobenzyl)-5-[1-(2-hydroxy-2-(adamant-1-yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole

5   1-(4-Cyanobenzyl)-5-[1-(2-acetyloxy-2-(adamant-1-yl)ethyl)-2-oxo-piperazin-4-yl-methyl]imidazole

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl] piperazine-4-(N-1-adamantyl)carboxamide

10   1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-(N-1-adamantyl)carbonyl piperazine

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-[N-(1R)-(-)-10-camphorsulfonyl]piperazine

15

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-(1-adamantylmethyl) piperazine

1-(4-Cyanobenzyl)-5-[1-(2-(adamant-1-yl)ethyl)-2-oxo-piperazin-4-20   yl-methyl]imidazole

1-(4-Cyanobenzyl)-5-[1-(1-(adamant-1-yl)methyl)-2-oxo-piperazin-4-yl-methyl]imidazole

25   1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl] piperazine-4-carboxylic acid (2-norbornane)methyl ester

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-piperazine-4-carboxylic acid (2-norbornane)methyl ester

30

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl] -4-(2-bicyclo-[2.2.2]-octylcarbonyl)piperazine

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-(2-norbornanecarbonyl)piperazine

1-[1-(4'-Cyanobenzyl) imidazol-5-ylmethyl]-4-cis/trans-(2,6,6-
5   trimethylbicyclo[3.1.1]heptanecarbonyl)-piperazine

1-(4'-Cyanobenzyl)-2-methyl-imidazol-5-ylmethyl piperazine-4-(N-1-adamantyl)carboxamide

10   or a pharmaceutically acceptable salt or optical isomer thereof.

9.   A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

15

10.   A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 8.

20   11.   A method for inhibiting farnesyl-protein transferase and geranylgeranyl-protein transferase type I which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

25   12.   A method for inhibiting farnesyl-protein transferase and geranylgeranyl-protein transferase type I which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

30   13.   A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

14.   A method according to Claim 13 wherein the cancer is characterized by a mutated K4B-Ras protein.

15.   A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

16.   A method according to Claim 15 wherein the cancer is characterized by a mutated K4B-Ras protein.

17.   A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

18.   A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

19.   A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

20.   A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

21.   A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

22.   A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

5   23.   A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

SEQUENCE LISTING

<110> Merck & Co., Inc.
        Lumma, William C. Jr.
        Smith, Anthony M.
        Sisko, John T.

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(54) Title: INHIBITORS OF PRENYL-PROTEIN TRANSFERASE

(57) Abstract: The present invention comprises piperazine-containing compounds which inhibit prenyl-protein transferases, including farnesyl-protein transferase and geranylgeranyl-protein transferase type I. Such therapeutic compounds are useful in the treatment of cancer.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/496, 31/551; A61P 13/12, 27/02, 31/12, 35/00; C12N 9/99; C07D 241/08, 243/08, 295/04, 295/06, 295/084, 403/04, 403/06, 403/12, 403/14

US CL : 514/218, 253.01, 253.09 254.05255.02, 255.03; 540/492, 575; 544/360, 364, 370, 380, 383, 403

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/218, 253.01, 253.09 254.05255.02, 255.03; 540/492, 575; 544/360, 364, 370, 380, 383, 403

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 2,410,492 A (GLAXO LABORATORIES, LTD.) 26 September 1974 (26.09.1974), page 20, see example 16 in Table II.	1, 9-23
X	US 5,055,468 A (GRAY ET AL) 08 October 1991 (08.10.1991) , column 31, see compound 3 in Table I.	1, 9-23
X	US 3,919,230 A (HILL ET AL) 11 November 1975(11.11.1975) column 4, see lines 55-64.	1, 9-23
X	TAKAYANAGI, I. et al. Newly synthesized a1-adenoceptor blockers (SM911 and SM 2470) and characterization of a-adenoceptors in rat aortic strips, rat vas deferens preparation and rabbit aortic strips, Gen. Pharmacol. 1985, Vol. 16, No. 6, pages 613-615, see Figure 1, compounds SM911 and SM2470.	1, 9-23
X	ZIKOLOVA et al. Synthesis of N1-substituted N4-guanylpiperazines, Tr. Nauchnoizsled. Khim.-Farm. Inst. 1982, Vol. 12, pages 47-55, especially see compounds II 12-16 pages 50-51.	1, 9-23
A	GELB, M.H. et al. Protein prenylation: from discovery to prospects for cancer treatment. Curr. Opin. Chem. Biol. February 1998, Vol. 2, No. 1, pages 40-48.	1-23

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier application or patent published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2000 (30.05.2000)	31 JUL 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Mark Berch, Ph. D. Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
                        ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 2–8,10,12, 15, 16 and parts of 1, 9, 11, 13, 14, and 17-23, drawn to piperazines.

Group II, claim(s) parts of 1, 9, 11, 13, 14, and 17-23, drawn to homopiperazines.

The inventions listed as Groups do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
The technical feature, which is mandatory for both groups, is a heterocyclic ring containing two nitrogen atoms linked to a polycyclic hydrocarbon ring. The heterocycle is six-membered in Group I and seven-membered in Group II.